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Metolachlor: Pesticide Registration Standards

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Office of
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Washington DC 20460

September 1980

Pesticides

EPA

2-chloro-N-(2-ethyl-6-methylphenyl -N-(2-methoxy-1-methylethyl) acetamide Metolachlor

Pesticide Registration Standard

EPA/~~OPP~~ SPRD - 80/520

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METOLACHLOR

2-chloro-N-(2-ethyl-6-methylphenyl)
-N-(2-methoxy-1-methylethyl acetamide

Pesticide Registration Standard

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HOW TO REGISTER
UNDER A REGISTRATION STANDARD

Organization of the Standard
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Requirement to Re-register Under the Standard
"Product Specific" Data and "Generic" Data
Data Compensation Requirements under FIFRA 3(c)(1)(D)
Obtaining Data to Fill "Data Gaps"; FIFRA 3(c)(2)(B)
Amendments to the Standard

Organization of the Standard

This first chapter explains the purpose of a Registration Standard and summarizes the legal principles involved in registering or re-registering under a Standard. The second chapter sets forth the requirements that must be met to obtain or retain registration for products covered by this particular Registration Standard. In the remaining chapters, the Agency reviews the available data by scientific discipline, discusses the Agency's concerns with the identified potential hazards, and logically develops the conditions and requirements that would reduce those hazards to acceptable levels.

Purpose of the Standard

Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) provides that "no person in any State may distribute, sell, offer for sale, hold for sale, ship, deliver for shipment, or receive (and having so received) deliver or offer to deliver, to any person any pesticide which is not registered with the Administrator [of EPA]." To approve the registration of a pesticide, the Administrator must find, pursuant to Section 3(c)(5) that:

"(A) its composition is such as to warrant the proposed claims for it;
(B) its labeling and other material required to be submitted comply with the requirements of this Act;
(C) it will perform its intended function without unreasonable adverse effects on the environment; and
(D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."

In making these findings, the Agency reviews a wide range of data which registrants are required to submit, and assesses the risks and benefits associated with the use of the proposed pesticide. But the established approach to making these findings has been found to be defective on two counts:

First, EPA and its predecessor agency, the United States Department of Agriculture (USDA), routinely reviewed registration applications on a 'product by product' basis, evaluating each product-specific application somewhat independently. In the review of products containing similar components, there was little opportunity for a retrospective review of the full range of pertinent data available in Agency files and in the public literature. Thus the 'product by product' approach was often inefficient and sometimes resulted in inconsistent or incomplete regulatory judgments.

Second, over the years, as a result of inevitable and continuing advances in scientific knowledge, methodology, and policy, the data base for many pesticides came to be considered inadequate by current scientific and regulatory standards. Given the long history of pesticide regulation in several agencies, it is even likely that materials may have been lost from the data files. When EPA issued new requirements for registration in 1975 (40 CFR 162) and proposed new guidelines for hazard testing in 1978 (43 FR 29686, July 10, 1978 and 43 FR 37336, August 22, 1978), many products that had already been registered for years were being sold and used without the same assurances of human and environmental safety as was being required for new products. Because of this inconsistency, Congress directed EPA to re-register all previously registered products, so as to bring their registrations and their data bases into compliance with current requirements [See FIFRA Section 3(g)].

Facing the enormous job of re-reviewing and calling-in new data for the approximately 35,000 current registrations, and realizing the inefficiencies of the 'product by product' approach, the Agency decided that a new, more effective method of review was needed.

A new review procedure has been developed. Under it, EPA publishes documents called Registration Standards, each of which discusses a particular pesticide active ingredient. Each Registration Standard summarizes all the data available to the Agency on a particular active ingredient and its current uses, and sets forth the Agency's comprehensive position on the conditions and requirements for registration of all existing and future products which contain that active ingredient. These conditions and requirements, all of which must be met to obtain or retain full registration or re-registration under Section 3(c)(5) of FIFRA, include the submission of needed scientific data which the Agency does not now have, compliance with standards of toxicity, composition, labeling, and packaging, and satisfaction of the data compensation provisions of FIFRA Section 3(c)(1)(D).

The Standard will also serve as a tool for product classification. As part of the registration of a pesticide product, EPA may classify each product for "general use" or "restricted use" [FIFRA Section 3(d)]. A pesticide is classified for "restricted use" when some special regulatory restriction is needed to ensure against unreasonable adverse effects to man or the environment. Many such risks of unreasonable adverse effects can be lessened if expressly-designed label precautions are strictly followed. Thus the special regulatory restriction for a "restricted use" pesticide is usually a requirement that it be applied only by, or under the supervision of, an applicator who has been certified by the State or Federal government as being competent to use pesticides safely, responsibly, and in accordance with label directions. A restricted-use pesticide can have other regulatory restrictions [40 CFR 162.11(c)(5)] instead of, or in addition to, the certified applicator requirement. These other regulatory restrictions may include such actions as seasonal or regional limitations on use, or a requirement for the monitoring of residue levels after use. A pesticide classified for "general use," or not classified at all, is available for use by any individual who is in compliance with State or local regulations. The Registration Standard review compares information about potential adverse effects of specific uses of the pesticide with risk criteria listed in 40 CFR 162.11(c), and thereby determines whether a product needs to be classified for "restricted use." If the Standard does classify a pesticide for "restricted use," this determination is stated in the second chapter.

Requirement to Re-register Under the Standard

FIFRA Section 3(g), as amended in 1978, directs EPA to re-register all currently registered products as expeditiously as possible. Congress also agreed that re-registration should be accomplished by the use of Registration Standards.

Each registrant of a currently registered product to which this Standard applies, and who wishes to continue to sell or distribute his product in commerce, must apply for re-regisration. His application must contain proposed labeling that complies with this Standard.

EPA will issue a notice of intent to cancel the registration of any currently registered product to which this Standard applies if the registrant fails to comply with the procedures for re-registration set forth in the Guidance Package which accompanies this Standard.

"Product Specific" Data and "Generic" Data

In the course of developing this Standard, EPA has determined the types of data needed for evaluation of the properties and effects of products to which the Standard applies, in the disciplinary areas of Product Chemistry, Environmental Fate, Toxicology, Residue Chemistry, and Ecological Effects. These determinations are based primarily on the data Guidelines proposed in 1978 (43 FR 29686, July 10, 1978, and 43 FR 37336, August 22, 1978), as applied to the use patterns of the products to which this Standard applies. Where it appeared that data from a normally applicable Guidelines requirement was actually unnecessary to evaluate these products, the Standard indicates that the requirement has been waived. On the other hand, in some cases studies not required by the Guidelines may be needed because of the particular composition or use pattern of products the Standard covers; if so, the Standard explains the Agency's reasoning. Data guidelines have not yet been proposed for the Residue Chemistry discipline, but the requirements for such data have been in effect for some time and are, the Agency believes, relatively familiar to registrants. Data which we have found are needed to evaluate the registrability of some products covered by the Standard may not be needed for the evaluation of other products, depending upon the composition, formulation type, and intended uses of the product in question. The Standard states which data requirements apply to which product categories. (See the second chapter.)

The various kinds of data normally required for registration of a pesticide product can be divided into two basic groups:

(A) data that is "product specific," i.e., data that relates only to the properties or effects of a product with a particular composition (or a group of products with closely similar composition); and

(B) "generic" data that pertains to the properties or effects of a particular ingredient, and thus is relevant to an evaluation of the risks and benefits of all products containing that ingredient (or all such products having a certain use pattern), regardless of any such product's unique composition.

The Agency requires certain "product specific" data for each product to characterize the product's particular composition and physical/chemical properties (Product Chemistry), and to characterize the product's acute toxicity (which is a function of its total composition). The applicant for registration or re-registration of any product, whether it is a manufacturing-use or end-use product, and without regard to its intended use pattern, must submit or cite enough of this kind of data to allow EPA to evaluate the product. For such purposes, "product specific" data on any product other than the applicant's is irrelevant, unless the other product is closely similar in composition to the applicant's. (Where it has been found practicable to group similar products for purposes of evaluating, with a single set of tests, all products in the group, the Standard so indicates.) "Product specific" data on the efficacy of particular end-use products is also required where the exact formulation may affect efficacy and where failure of efficacy could cause public health problems.

All other data needed to evaluate pesticide products concerns the properties or effects of a particular ingredient of products (normally a pesticidally active ingredient, but in some cases a pesticidally inactive, or "inert," ingredient). Some data in this "generic" category are required to evaluate the properties and effects of all products containing that ingredient [e.g., the acute LD-50 of the active ingredient in its technical or purer grade; see proposed 40 CFR 163.81-1(a), 43 FR 37355].

Other "generic" data are required to evaluate all products which both contain a particular ingredient and are intended for certain uses (see, e.g., proposed 40 CFR 163.82-1, 43 FR 37363, which requires subchronic oral testing of the active ingredient with respect to certain use patterns only). Where a particular data requirement is use-pattern dependent, it will apply to each end-use product which is to be labeled for that use pattern (except where such end-use product is formulated from a registered manufacturing-use product permitting such formulations) and to each manufacturing-use product with labeling that allows it to be used to make end-use products with that use pattern. Thus, for example, a subchronic oral dosing study is needed to evaluate the safety of any manufacturing-use product that legally could be used to make an end-use, food-crop pesticide. But if an end-use product's label specified it was for use only in ways that involved no food/feed exposure and no repeated human exposure, the subchronic oral dosing study would not be required to evaluate the product's safety; and if a manufacturing-use product's label states that the product is for use only in making end-use products not involving food/feed use or repeated human exposure, that subchronic oral study would not be relevant to the evaluation of the manufacturing-use product either.

If a registrant of a currently registered manufacturing-use or end-use product wishes to avoid the costs of data compensation [under FIFRA Section 3(c)(1)(D)] or data generation [under Section 3(c)(2)(B)] for "generic" data that is required only with respect to some use patterns, he may elect to delete those use patterns from his labeling at the time he re-registers his product. An applicant for registration of a new product under this Standard may similarly request approval for only certain use patterns.

Data Compensation Requirements under FIFRA 3(c)(1)(D)

Under FIFRA Section 3(c)(1)(D), an applicant for registration, re-registration, or amended registration must offer to pay compensation for certain existing data the Agency has used in developing the Registration Standard. The data for which compensation must be offered is all data which is described by all the following criteria:

(1) the data were first submitted to EPA (or to its predecessor agencies, USDA or FDA), on or after January 1, 1970;

(2) the data were submitted to EPA (or USDA or FDA) by some other applicant or registrant in support of an application for an

experimental use permit, an amendment adding a new use to a registration, or for re-registration, or to support or maintain in effect an existing registration;

(3) the data are relevant to the Agency's decision to register or re-register the applicant's product under the Registration Standard, taking into account the applicant's product's composition and intended use pattern(s);

(4) the data are determined by EPA to be valid and usable in reaching regulatory conclusions; and

(5) the data are not those for which the applicant has been exempted by FIFRA Section 3(c)(2)(D) from the duty to offer to pay compensation. (This exemption applies to the "generic" data concerning the safety of an active ingredient of the applicant's product, not to "product specific" data. The exemption is available only to applicants whose product is labeled for end-uses for which the active ingredient in question is present in the applicant's product because of his use of another registered product containing that active ingredient which he purchases from another producer.)

An applicant for re-registration of an already registered product under this Standard, or for registration of a new product under this Standard, accordingly must determine which of the data used by EPA in developing the Standard must be the subject of an offer to pay compensation, and must submit with his application the appropriate statements evidencing his compliance with FIFRA Section 3(c)(1)(D).

An applicant would never be required to offer to pay for "product specific" data submitted by another firm. In many, if not in most cases, data which are specific to another firm's product will not suffice to allow EPA to evaluate the applicant's product, that is, will not be useful to the Agency in determining whether the applicant's product is registrable. There may be cases, however, where because of close similarities between the composition of two or more products, another firm's data may suffice to allow EPA to evaluate some or all of the "product specific" aspects of the applicant's product. In such a case, the applicant may choose to cite that data instead of submitting data from tests on his own product, and if he chooses that option, he would have to comply with the offer-to-pay requirements of Section 3(C)(1)(D) for that data.

Each applicant for registration or re-registration of a manufacturing-use product, and each applicant for registration or re-registration of an end-use product, who is not exempted by FIFRA Section 3(c)(2)(D), must comply with the Section 3(c)(1)(D) requirements with respect to each item of "generic" data that relates to his product's intended uses.

A detailed description of the procedures an applicant must follow in applying for re-registration (or new registration) under this Standard is found in the Guidance Package for this Standard.

Obtaining Data to Fill "Data Gaps"; FIFRA 3(c)(2)(B)

Some of the kinds of data EPA needs for its evaluation of the properties and effects of products to which this Standard applies have never been submitted to the Agency (or, if submitted, have been found to have deficiencies rendering them inadequate for making registrability decisions) and have not been located in the published literature search that EPA conducted as part of preparing this Standard. Such instances of missing but required data are referred to in the Standard as "data gaps".

FIFRA Section 3(c)(2)(B), added to FIFRA by the Congress in 1978, authorizes EPA to require registrants to whom a data requirement applies to generate (or otherwise produce) data to fill such "gaps" and submit those data to EPA. EPA must allow a reasonably sufficient period for this to be accomplished. If a registrant fails to take appropriate and timely steps to fill the data gaps identified by a section 3(c)(2)(B) order, his product's registration may be suspended until the data are submitted. A mechanism is provided whereby two or more registrants may agree to share in the costs of producing data for which they are both responsible.

The Standard lists, in its summary second chapter, the "generic" data gaps and notes the classes of products to which these data gaps pertain. The Standard also points out that to be registrable under the Standard, a product must be supported by certain required "product specific" data. In some cases, the Agency may possess sufficient "product specific" data on one currently registered product, but may lack such data on another. Only those Standards which apply to a very small number of currently registered products will attempt to state definitively the "product specific" data gaps on a 'product by product' basis. (Although the Standard will in some cases note which data that EPA does possess would suffice to satisfy certain "product specific" data requirements for a category of products with closely similar composition characteristics.)

As part of the process of re-registering currently registered products, EPA will issue Section 3(c)(2)(B) directives requiring the registrants to take appropriate steps to fill all identified data gaps -- whether that data in question is "product specific" or "generic" -- in accordance with a schedule.

Persons who wish to obtain registrations for new products under this Standard will be required to submit (or cite) sufficient "product specific" data before their applications are approved. Upon registration, they will be required under Section 3(c)(2)(B) to take appropriate steps to submit data needed to fill "generic" data gaps. (We expect they will respond to this requirement by entering into cost-sharing agreements with other registrants who previously have been told they must furnish the data.) The Guidance Package for this Standard details the steps that must be taken by registrants to comply with Section 3(c)(2)(B).

Amendments to the Standard

Applications for registration which propose uses or formulations that are not presently covered by the Standard, or which present product compositions, product chemistry data, hazard data, toxicity levels, or labeling that do not meet the requirements of the Standard, will automatically be considered by the Agency to be requests for amendments to the Standard. In response to such applications, the Agency may request additional data to support the proposed amendment to the Standard, or may deny the application for registration on the grounds that the proposed product would cause unreasonable adverse effects to the environment. In the former case, when additional data have been satisfactorily supplied, and providing that the data do not indicate the potential for unreasonable adverse effects, the Agency will then amend the Standard to cover the new registration.

Each Registration Standard is based upon all data and information available to the Agency's reviewers on a particular date prior to the publication date. This "cut-off" date is stated at the beginning of the second chapter. Any subsequent data submissions and any approved amendments will be incorporated into the Registration Standard by means of addenda, which are available for inspection at EPA in Washington, D.C., or copies of which may be requested from the Agency. When all the present "data gaps" have been filled and the submitted data have been reviewed, the Agency will revise the Registration Standard. Thereafter, when the Agency determines that the internally maintained addenda have significantly altered the conditions for registration under the Standard, the document will be updated and re-issued for publication.

While the Registration Standard discusses only the uses and hazards of products containing the designated active ingredient(s), the Agency is also concerned with the potential hazards of some inert ingredients and impurities. Independent of the development of any one Standard, the Agency has initiated the evaluation of some inert pesticide ingredients. Where the Agency has identified inert ingredients of concern in a specific product to which the Standard applies, these ingredients will be pointed out in the Guidance Package.

REQUIREMENTS FOR METOLACHLOR PRODUCTS

The following is the Agency's position on the present requirements for registration and re-registration under this Metolachlor Registration Standard, including: (1) what 'standards' of composition, acute toxicity, physical and chemical properties, use, labeling, and packaging will ensure the safe use of the pesticide active ingredient Metolachlor; and (2) what studies are needed to retain existing registrations and to complete the data base that will support future registrations under the Metolachlor Standard. There are different 'standards' and data requirements for technical (manufacturing-use) Metolachlor and for emulsifiable concentrate (end-use) Metolachlor. Producers who use an 'integrated formulation system' to manufacture a Metolachlor end-use product are responsible for the data required for both a manufacturing-use and an end-use product.

This Registration Standard is based on all pertinent data and information on Metolachlor available to the Agency's reviewers as of June 30, 1980.

Metolachlor

'Metolachlor' [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] is a selective herbicide used as either a pre-plant incorporated or pre-emergence surface applied treatment for the control of most annual grasses and certain broadleaf weeds in field corn (except fresh corn and popcorn), soybeans, peanuts, and grain sorghum.

There is presently only one registrant and data submitter for pesticide products containing Metolachlor: Ciba-Geigy Corporation (Agricultural Division, P.O. Box 11422, Greensboro, North Carolina, 27409).

The three presently registered products containing Metolachlor as the sole active ingredient are a manufacturing-use 'technical' and two emulsifiable concentrate formulations, one containing 8 pounds of active ingredient per gallon, and the other containing 6 pounds per gallon. The formulation containing 6 pounds active ingredient per gallon is not presently in production, although a small quantity remains on the market for 1980. Metolachlor is also marketed in a package mix with each of two other herbicides, 'Atrazine' and 'Propazine', and is often mixed by the applicator with other herbicides to provide a broader spectrum of weed control. However, please note that this Metolachlor Standard will only consider the registration of products which contain Metolachlor as the sole active ingredient, and will only consider those potential hazards which arise from Metolachlor applied alone.

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TECHNICAL METOLACHLOR

In order to be registrable under this Standard, a Technical Metolachlor product must comply with the following standards of composition, purity, and toxicity: A Technical Metolachlor should contain at least 90 % (by weight) the active ingredient 'Metolachlor', i.e. 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide. If the manufacturing process submitted is found by the Agency to be substantially different from the one used to produce the presently registered Technical Metolachlor, a theoretical discussion concerning the formation of unintentional ingredients will have to be submitted to attest that potentially harmful impurities will not result (see Proposed Guidelines 163.61-5). The "product specific" acute toxicology testing on a Technical Metolachlor (or on a "substantially similar" Technical Metolachlor) must demonstrate that it falls into Toxicity Categories which are the same as or numerically higher than the following:

Acute Oral Toxicity: Category III
Acute Dermal Toxicity: Category III
Acute Inhalation Toxicity: Category III
Primary Eye Irritation: Category III
Primary Dermal Irritation: Category III

The following 'Sample Label' includes all those labeling statements which the Agency has determined will provide an adequate mitigation of those hazards to man and the environment which may result from the handling, transport, re-formulation, storage, or disposal of Technical Metolachlor. In order to be registered under this Standard, therefore, a Technical Metolachlor must meet the following standard for labeling by submitting a label which includes these statements in an appropriate format. [Consult the Proposed Guidelines Section 162.10 for more complete directions on formats for labeling.]

PRODUCT NAME

For Formulation of Herbicides Only

Active Ingredient:
Metolachlor: 2-chloro-N-(2-ethyl-6-methylphenyl)-
N-(2-methoxy-1-methylethyl)acetamide ......%
Inert Ingredients: ......%
Total: 100%

CAUTION

PRECAUTIONARY STATEMENTS:

Hazards to Humans and Domestic Animals: Harmful if swallowed. May cause skin sensitization. Wear protective clothing (coveralls and gloves) while handling and using this product. Wash thoroughly after handling. Remove and wash contaminated clothing before re-use.
Statement of Practical Treatment: If swallowed, drink one or two glasses of water. Induce vomiting by placing finger in back of throat. Call a physician. Never give anything by mouth to an unconscious person. If in eyes or on skin, flush with plenty of water. If irritation persists, call a physician.
Hazards to Wildlife: Do not discharge into lakes, streams, ponds, or public waters unless in accordance with an NPDES permit. For guidance, contact your regional office of EPA.

DIRECTIONS FOR USE

Refer to technical bulletin. It is a violation of federal law to use this product in a manner inconsistent with its labeling.

STORAGE AND DISPOSAL

For bulk shipments in holding tanks, tank cars, storage tanks, etc.:
Do not contaminate water, food, or feed by storage or disposal. Open dumping or open burning is prohibited. Pesticide or rinsate that cannot be used, recycled, or chemically reprocessed and tanks that cannot be re-used should be disposed of in a landfill disposal site approved for pesticides. Thoroughly clean containers before re-use. Consult federal, state, or local disposal authorities for approved alternative measures.

For metal drums, cans, etc.:
Do not contaminate water, food, or feed by storage or disposal. Open dumping or open burning is prohibited. Re-seal container and offer for re-conditioning; or triple rinse (or equivalent) and offer for recycling or re-conditioning. Pesticide or rinsate that cannot be used, recycled, or chemically re-processed, and containers that cannot be re-used or recycled should be disposed of in a landfill disposal site approved for pesticides. Consult federal, state, or local disposal authorities for approved alternative measures.

Note to Formulators: formulators are responsible for providing data to support the registration of products formulated from this Technical.

EPA Registration No. ____________ Net Wt. or Measure ________________
Establishment No. ____________
Name and Address of the producer, registrant, or person for whom produced.

Finally, in order to re-register Technical Metolachlor under this Standard, each registrant is required to submit or cite all the data below. The Product Chemistry data are "product specific" studies specific to the currently registered Technical Metolachlor; the Environmental Fate, Toxicology, and Ecological Effects data are "generic" studies that would test the active ingredient or a typical formulation in order to assess the hazards due to end-uses. After each is listed the section in the Proposed Guidelines (43 FR 29686, July 10, 1978, and 43 FR 37336, August 2, 1978) which describes that type of data and what test substances should be used.

Product Chemistry

1)	Octanol/Water Partition Coefficient;	163.61-8(c)6
2)	Flammability;	163.61.8(c)13
3)	Oxidizing or Reducing Action;	163.61-8(c)14
4)	Explosiveness;	163.61-8(c)15
5)	Viscosity;	163.61-8(c)17
6)	Corrosion Characteristics;	163.61-8(c)18
7)	(and, if Technical Metolachlor is shown to produce genetic effects in future testing:) An analytical method (or reference to a method) for detecting and measuring each identifiable impurity (associated with the manufacturing of the Technical) in the formulated products of Metolachlor;	163.61-7

Environmental Fate

8)	Adsorption/desorption studies;	163.62-9
9)	Actual field-use residue monitoring studies at two watershed sites to be approved by the Agency;	(not discussed in the Proposed Guidelines)
10)	Accumulation studies on rotational crops for small grains, root crops, and leafy vegetables;	163.61-11(b)

Toxicology

11)	Subchronic Oral Dosing - Pathological evaluation for both the rat and dog;	163.82-1
12)	Chronic Feeding - A chronic feeding study on laboratory rat;	163.83-1
13)	Oncogenicity - Completion of the mouse study; and testing on a mammal other than the mouse (the laboratory rat is preferred), or an oncogenic evaluation for the chronic feeding study [see (12) above];	163.83-2
14)	Teratology - A teratology study in a mammalian species other than the rat;	163.83-3
15)	Reproduction - A multi-generation reproduction study on one mammalian species (preferably the laboratory rat);	163.83-4

Ecological Effects

16)	Activated sludge metabolism study;	163.62-8(g)
17)	The avian acute oral LD-50 for one species of waterfowl (preferably the mallard) or one species of upland game bird (preferably the bobwhite quail); the species must be one of those for which an LC-50 was determined under FR 163.71-2.	163.71-1

EMULSIFIABLE CONCENTRATE METOLACHLOR

In order to be registrable under this Registration Standard, an end-use pesticide product containing Metolachlor must contain Metolachlor as the sole pesticide active ingredient. The only end-use Metolachlor formulations registrable under this Standard are Emulsifiable Concentrates of Metolachlor, which are liquids consisting of the active ingredient suspended or dissolved in one or more water-insoluble organic solvents, and if necessary, stabilized by an emulsifying agent. The strength of each Metolachlor Emulsifiable Concentrate must be stated in pounds Metolachlor per gallon liquid.

In order to registrable under this Standard, the "product specific" acute toxicology testing on a Metolachlor Emulsifiable Concentrate (or a "substantially similar" one) must demonstrate that it falls into Toxicity Categories which are the same as or numerically higher than the following:

Acute Oral Toxicity: Category II
Acute Dermal Toxicity: Category III
Acute Inhalation Toxicity: Category II
Primary Eye Irritation: Category I
Primary Dermal Irritation: Category II

In order to be registrable under this Standard, the "product specific" product chemistry testing on a Metolachlor Emulsifiable Concentrate must show that it has physical/chemical properties which fall within the limits listed below. For physical/chemical properties which are not shown below (see the Product Chemistry chapter), no Standard has been set.

Physical State: liquid at room temperature
Vapor Pressure: between 0.05 and 1.0 mm Hg at 20°C
pH: between 6 and 8
Flammability: flashpoint above 80°F
Explosiveness: does not form explosive mixtures and is not shock sensitive
Corrosiveness: must be no more than slightly corrosive to steel or tin

These acute toxicity and physical/chemical properties tests need not be performed for a proposed Emulsifiable Concentrate if it is substantially similar to a previously registered Metolachlor Emulsifiable Concentrate. The applicant may request the Agency, in writing, to consider, by examination of the statements of formula, whether the proposed product qualifies as 'substantially similar' to a previously registered product.

In order to be registrable under this Standard, a Metolachlor Emulsifiable Concentrate product must bear labeling in compliance with the following, and where appropriate, with label statements which are correctly correlated with the product's toxicity categories or physical/chemical properties. [Consult 40 CFR Section 162.10 for more complete directions on formats for labeling.]

1) The PRODUCT NAME at the top of the front panel;
2) Beneath the name, the product type "Herbicide";
3) A general statement of the product's use: "For weed control in field corn (except fresh corn and popcorn), soybeans, grain sorghum, and peanuts", or any one or combination of these crops;
4) A front panel statement of the ingredient percentages:
    Active Ingredient:
    Metolachlor: 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide ..... %
    Inert Ingredients: ..... %
    Total: 100 %
5) Directly below the ingredient statement, the statement "PRODUCT NAME contains ( ) pounds active ingredient per gallon";
6) A human hazard signal word on the front panel, selected as follows:
    If the Primary Eye Irritation is Category I: DANGER
    If the highest Toxicity Category is II: WARNING
    If the highest Toxicity Category is III or IV: CAUTION
7) Just above the signal word, the statement "Keep out of reach of children".
8) Under the heading, "PRECAUTIONARY STATEMENTS", (preferably on front panel, but if not, then print on front panel, below the signal word: "See side panel for additional precautionary statements"):
    Under the heading, "Hazards to Humans and Domestic Animals":
        The human hazard signal word [same as (6) above];
        For acute oral toxicity,
            if Category II: "May be fatal if swallowed."
            if Category III: "Harmful if swallowed."
            if Category IV: no statement required
        For acute dermal toxicity,
            if Category III: "Harmful if absorbed through skin. Avoid contact with skin or clothing."
            if Category IV: no statement required
        For acute inhalation toxicity,
            if Category II: "May be fatal if inhaled. Do not breathe vapors or spray mist."
            if Category III: "Harmful if inhaled. Avoid breathing vapors or spray mist."
            if Category IV: no statement required
        For primary eye irritation,
            if Category I: "Corrosive, causes eye damage. Do not get in eyes. Wear goggles or face shield when handling."
            if Category II: "Causes eye irritation. Do not get in eyes."

if Category III: "Avoid contact with eyes. In case of contact immediately flush eyes or skin with plenty of water. Get medical attention if irritation persists."

if Category IV: no statement required

For primary dermal irritation,

if Category II: "Causes skin irritation. Do not get on skin or on clothing."

if Category III: "Avoid contact with skin or clothing. In case of contact, immediately flush skin with plenty of water. Get medical attention if irritation persists."

if Category IV: no statement required

For dermal sensitization,

"May cause skin sensitization. Wear gloves and protective clothing while handling or using this product. Wash thoroughly after handling. Remove and wash contaminated clothing before re-use."

Under the heading, "Environmental Hazards":

"Avoid direct application to any body of water. Do not apply where runoff is likely to occur. Do not contaminate water by cleaning of equipment or disposal of wastes. Do not apply when weather conditions favor drift from target area."

Under the heading, "Physical/Chemical Hazards":

For flammability, if the flash point is above 80°F and not over 150°F, the statement: "Do not use or store near heat or open flame".

For corrosiveness, if corrosive to steel or tin, the statement: "Do not place in unlined metal containers or tanks."

And beside the heading, "First Aid":

If the formulation has greater than 10% by weight petroleum distillates, and has Category IV Acute Oral Toxicity:

"In case of contact with eyes, immediately flush with plenty of water for at least 15 minutes. Call a physician. If inhalation occurs, the victim should be moved to fresh air, and medical attention should be sought. If swallowed contact your local Poison Control Center, hospital, or physician immediately. If patient is unconscious, maintain breathing and heartbeat (CPR: cardiopulmonary resuscitation). Do not induce vomiting! [Note to Physician: If swallowed, there is no specific antidote. The use of emesis and/or lavage should be weighed against the possibility of a chemical pneumonitis as this product contains petroleum distillates. Treat symptomatically! The use of an aqueous slurry of activated charcoal (such as Norit A) and a saline cathartic should be considered.]"

If the formulation has greater than 10% by weight petroleum distillates, and has Category II or III Acute Oral Toxicity:

"In case of contact with eyes, immediately flush with plenty of water for at least 15 minutes. Call a physician. If inhalation occurs, the victim should be moved to fresh air, and medical attention should be sought. If swallowed contact your local Poison Control Center, hospital, or physician immediately ..." [The remainder of this First Aid statement, which will concern the use of emesis and/or lavage, will be determined at the time of (re-)registration, and will be based on the precise quantitative toxicity of the formulation. See the NOTE below.]

If the formulation contains, by weight, 10% or less (or does not contain) petroleum distillates:

"In case of contact with eyes, immediately flush with plenty of water for at least 15 minutes. Call a physician. If inhalation occurs, the victim should be moved to fresh air, and medical attention should be sought. If swallowed, contact your local Poison Control Center, hospital, or physician immediately. If patient is unconscious, maintain breathing and heartbeat (CPR: cardiopulmonary resuscitation). If patient is conscious, induce vomiting (syrup of ipecac; if not available, stimulate back of throat with finger). Never give anything by mouth to an unconscious person! [Note to Physician: If swallowed, there is no specific antidote. Induce emesis and lavage stomach. Treat symptomatically! The use of an aqueous slurry of activated charcoal (such as Norit A) and a saline cathartic should be considered.]

9) After precautionary statements, under "DIRECTIONS FOR USE":

The statement:

"It is a violation of Federal law to use this product in a manner inconsistent with its labeling."

The statement (required for agricultural-use pesticides):

"This product must be applied in accordance with 40 CFR Part 170."

"Under the heading, "General Information":

"PRODUCT NAME [( ) lbs. a.i./gal.] is a selective herbicide recommended as a preplant incorporated or pre-emergence surface-applied treatment in water or fluid fertilizer for control of most annual grasses and certain broadleaf weeds in corn grown for grain (except popcorn), soybeans, peanuts, and grain sorghum", or any one or combination of these crops. When corn is listed as one of these crops, "Do not use on sweet corn or popcorn." Also, the statement: "Failure to follow all precautions on this label may result in poor weed control, crop injury, or illegal residues."

Also include, where spraying equipment if discussed:

"Use conventional ground sprayers or center pivot irrigation application" and any additional directions or precautions for using these methods of application.

10) Under the heading, "PRODUCT NAME Applied Alone":

If for use on corn, under the heading, "Corn":

Directions should specify all application methods and rates. All applications must be pre-emergence. No rate in excess of 6 pounds active ingredient per acre may be recommended.

If for use on soybeans, under the heading, "Soybeans":
Directions should specify all application methods and rates. All applications must be pre-emergence. No rate in excess of 3 pounds active ingredient per acre may be recommended.

If for use on peanuts, under the heading, "Peanuts":
Directions should specify all application methods and rates. All applications must be pre-emergence. No rate in excess of 3 pounds active ingredient per acre may be recommended.

If for use on sorghum, under the heading, "Grain Sorghum":
Directions should specify all application methods and rates. All applications must be pre-emergence. No rate in excess of 2-1/2 pounds active ingredient per acre may be recommended. (If the product will severely injure the crop when the sorghum seed is not pre-treated, it is advisable to include a statement to this effect.)

(When application methods and rates are the same for two or more crops, these directions may be listed under a combined heading such as "Corn and Soybeans".)

Under the heading, "Rotational Crops":
"1) If crop treated with PRODUCT NAME is lost, corn, soybeans, peanuts, or grain sorghum may be replanted immediately. Do not make a second application of PRODUCT NAME. If the original application was banded, and the second crop is planted in the untreated row middles, a second banded treatment may be applied. 2) Small grains may be planted 4-1/2 months following treatment. Field corn (except fresh corn and popcorn), cotton, soybeans, peanuts, sorghum, root crops, and small grains may be planted in the spring following treatment. Do not graze or feed forage or fodder from cotton or small grains to livestock. All other rotational crops may be planted 18 months after application."

11) Under the heading, "STORAGE AND DISPOSAL":

Concerning disposal,
"Open dumping or open burning is prohibited. Do not re-use empty container; triple rinse or equivalent. Pesticide or rinsate that cannot be used, recycled, or chemically reprocessed, and triple-rinsed containers with their rinsate, should be disposed of in a landfill disposal site approved for pesticides. Consult federal, state, or local disposal authorities for approved alternative procedures."

Concerning storage,
the statement: "Keep out of reach of children";
if the flash point is above 80°F and not over 150°F, the statement: "Do not store near heat or open flame.";
if the product is corrosive to steel or tin, the statement: "Do not store in unlined containers or tanks.";

12) The label must also bear the 'EPA Registration Number', the "Net Weight or Measure" of the contents of the container, and the Name and Address of the producer, registrant, or person for whom the product was produced. Finally, the "Establishment Number" should appear on either the label or the container.

NOTE: Concerning labeling for products containing petroleum distillates, proper emergency medical treatment for the ingestion of petroleum distillates is a controversial subject. Two significant risks must be weighed in reaching a decision on whether or not to induce emesis or perform gastric lavage: If emesis is induced, or gastric lavage is performed, petroleum distillates may be aspirated, possibly resulting in fatal chemical pneumonitis. However, retaining a highly toxic pesticide in the stomach even for a short period of time may also prove fatal.

The Agency has contacted a number of authorities both within and outside EPA. There is no general agreement on how this problem may best be solved. In reaching a decision on appropriate labeling policy for products, the Agency considers the toxic properties of the active ingredients, inerts, and impurities. Thus, labeling requirements may differ for chemicals and products addressed in these Standards.

In establishing a policy, the Agency has considered that emergency treatment may not be readily available, and that first aid will usually be administered by a member of the general public who has little or no medical training.

In general the Agency believes that the best advice is to seek medical help immediately and to keep the patient breathing until medical help arrives. The Agency believes the following labeling is appropriate for all products which contain more than 10% by weight petroleum distillates:

(1) "If patient is unconscious, maintain breathing and heartbeat (CPR: cardiopulmonary resuscitation). Contact your local Poison Control Center, hospital, or physician immediately."

Pesticides in Acute Oral Toxicity Category I have an acute LD-50 of less than or equal to 50 mg/kg, and a seriously toxic dose of such a pesticide could readily be swallowed by both a 70 kg adult (a dose of 3.5 gm) and a 12 kg child (a dose of 0.6 gm). Thus for all products that contain more than 10% by weight petroleum distillates and are in Oral Toxicity Category I, it is prudent to recommend in addition to Statement (1):

> "If patient is conscious, induce vomiting (syrup of ipecac; if not available, stimulate back of throat with finger). Never give anything by mouth to an unconscious person!"

Pesticides in Acute Oral Toxicity Category IV have an acute LD-50 of greater than 5 g/kg, and a seriously toxic dose could not readily be swallowed by either a 70 kg adult (a dose of 350 gm) or a 12 kg child (a dose of 60 gm). Thus, because the risk of chemical pneumonitis following emesis is greater than the risk of allowing the pesticide to remain in the system, for all products which contain more than 10% by weight petroleum distillates and are in Oral Toxicity Category IV, the label should say in addition to Statement (1):

> "Do not induce vomiting!"

Products in Oral Toxicity Categories II and III, which could have an acute LD-50 anywhere between 50 and 5000 mg/kg, will be dealt with on a product by product basis at the time of registration or re-registration, and label statements will be based on a review of the toxicity of active ingredient(s), inerts, and impurities.

The Agency has determined that the above 'Standards' adequately limit the acute hazards of Emulsifiable Concentrate Metolachlor for agricultural workers and others not directly involved in the application, and that therefore no reentry interval has been established for Emulsifiable Concentrate Metolachlor. Nevertheless, users should be aware that the "application of a pesticide in such a manner as to directly or through drift expose workers or other persons except those knowingly involved in the application" is expressly prohibited under 40 CFR 170.3. Registrants may amplify the statement on labels or labeling to "apply in a accordance with 40 CFR Part 170" by stating the requirements of 40 CFR Part 170 or additions thereto if they so choose.

Finally, the following are "product specific" studies needed to complete the data base which will support the re-registration of currently registered Emulsifiable Concentrates under this Standard. In order to re-register the following Metolachlor Emulsifiable Concentrates under this Standard, each registrant is required to submit or cite these data. After each requirement is listed the section in the Proposed Guidelines which describes that type of data and what test substances should be used.

For currently registered Emulsifiable Concentrate Metolachlor of six (6) pounds active ingredient per gallon:

Product Chemistry	
1) Color	163.61-8(c)1
2) Odor	163.61-8(c)2

For currently registered Emulsifiable Concentrate Metolachlor of eight (8) pounds active ingredient per gallon:

Product Chemistry	
1) Color	163.61-8(c)1
2) Odor	163.61-8(c)2
3) Explosiveness	163.61-8(c)15
Toxicology	
4) Acute inhalation toxicity study.	163.81-3

USE PROFILE

The currently registered end-use formulations of Metolachlor are two Emulsifiable Concentrates, one at six pounds active ingredient per gallon, the other at eight pounds per gallon. Metolachlor is a selective herbicide, used either as a pre-plant incorporated or pre-emergence surface-applied treatment in water or fluid fertilizer for the control of most annual grasses and certain broadleaf weeds in field corn (except fresh corn and popcorn), soybeans, peanuts, and grain sorghum. This Registration Standard for Metolachlor only considers the risks that arise from the use of Metolachlor alone, and not when it is formulated or tank mixed with other pesticides. Application for Metolachlor alone is performed as follows for presently registered products:

pre-plant incorporated - 1.5 to 3.0 pounds active ingredient per acre (1.5 to 2.5 lbs. ai/acre for grain sorghum) (depending upon soil type), used when field has furrow irrigation, or when a period of dry weather is expected. Fourteen days before planting, (but after bed formation if the corn or soybeans are to be planted on beds), the chemical is diluted appropriately with water or fluid fertilizer, applied to the soil by conventional ground sprayer (or center pivot irrigation system), and incorporated into the top 2 inches of soil. A finishing disc, harrow, rolling cultivator, or similar implement is used to provide a uniform 2 inch incorporation.

pre-emergence surface-applied - 1.5 to 3.0 pounds active ingredient per acre (1.5 to 2.5 lbs. ai/acre for grain sorghum) (depending upon soil type), applied by conventional ground sprayer (or center pivot irrigation system) during planting (behind the planter), or after planting but before weeds or crop emerge.

The directions for application to sorghum fields require that grain sorghum be treated with Metolachlor alone only when the seed have been pre-treated with 'Concep' (registered trademark of CIBA-GEIGY) at 8 oz./100 lbs. of seed, which blocks the herbicidal action of Metolachlor on sorghum.

The registered rotational crops restriction is: small grains may be planted 4-1/2 months following treatment; field corn (except fresh corn and popcorn), soybeans, cotton, peanuts, grain sorghum, root crops, and small grains may be planted the spring following treatment; do not graze or feed forage or fodder from small grains to livestock; all other crops may be planted 18 months after application without restriction.

Studies which examine the use of a pesticide in integrated pest management (IPM) schemes may suggest ways of reducing application rates or frequency for pesticide chemicals, without reducing the degree of pest control achieved. IPM schemes may put the reduced use of a chemical in conjunction with one or more of the following biological and cultural methods of control: the development of resistant varieties of host plants and animals, the introduction of natural enemies, adjustments in crop rotations, cropping systems and planting time, water management and tillage practices, and the diagnostic techniques for evaluating the degree of pest infestation so that the chemical is used only when needed. Information about the use of Metolachlor in IPM schemes is expected to become available as more IPM weed control schemes are developed, and the Standard for Metolachlor will then consider the degree to which hazards are lowered by these alternative, but equally effective, uses of the chemical.

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PRODUCT CHEMISTRY

INTRODUCTION

FIFRA 3(c)(2)(A) requires the Agency to establish guidelines for registering pesticides in the United States. The Agency requires registrants to provide quantitative data on all added ingredients, active and inert, which are equal to or greater than 0.1% of the product by weight.

To establish the composition of products proposed for registration, the Agency requires not only data and information on the manufacturing and formulation processes, but also a discussion on the formation of manufacturing impurities and other product ingredients, intentional and unintentional. Further, to assure that the composition of the product as marketed will not vary from the composition evaluated at the time of registration, applicants are required to submit a statement certifying upper and lower composition limits for the added ingredients, or only upper limits for some unintentional ingredients. Subpart D suggests specific precision limits for ingredients based on the percentage of ingredient and the standard deviation of the analytical method.

In addition to the data on product composition, the Agency also requires data to establish the physical and chemical properties of both the pesticide active ingredient and its formulations (FR 163.61-10). For example, data are needed concerning the identity and physical state of the active ingredient (e.g., melting and boiling point data, vapor pressure, and solubility). Data are also required on the properties of the formulated product to establish labeling cautions (e.g., flammability, corrosivity, and storage stability). The Agency uses these data to characterize each pesticide and to determine its environmental and health hazards.

TOPICAL DISCUSSIONS

Corresponding to each of the Topical Discussions listed below is the number of the section in the 'Proposed Guidelines for Registering Pesticides' of July 10, 1978 (FR Part 163), which explains the data that the Agency will need in order to assess Metolachlor's Product Chemistry.

	Guidelines Section
Chemical Identity	163.61-3
Manufacturing Process	163.61-4
Percentages of Components in Pesticide Products	163.61-6
Product Analytical Methods and Data	163.61-7
Physical/Chemical Properties	163.61-8

Chemical Identity

'Metolachlor' is the acceptable common name for 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide as determined by the American National Standards Institute (1975). Ciba-Geigy Corporation, presently the sole manufacturer of Metolachlor in the United States, has assigned Metolachlor the experimental number 'CGA-24705' (for the active ingredient), and the trade name 'Dual'. The name 'Metolachlor' will be used in the Standard in place of the trade name or the chemical name.

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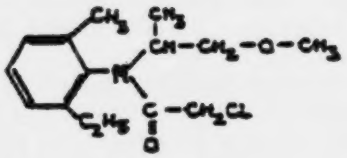
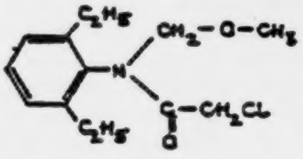
METOLACHLOR AND RELATED
HERBICIDES



Metolachlor



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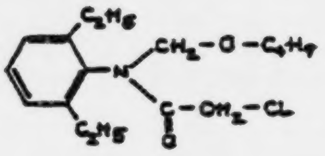

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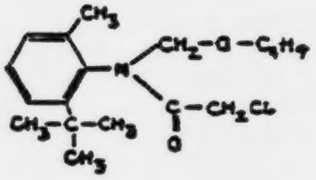

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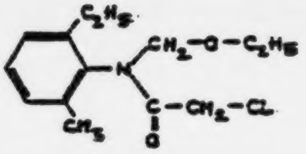

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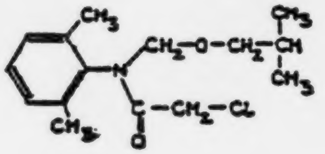

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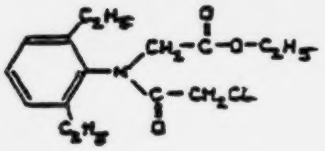
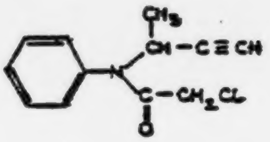
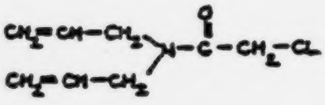


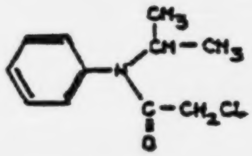
Diethathyl-ethyl



Prynachlor



Allidochlor



Propachlor

FIGURE 1.1

Metolachlor is both a 2-chloroacetamide and a 2-chloroacetanilide. Figure 1.1 shows the relationship between Metolachlor and other pesticide active ingredients similar in chemical structure. See the 'Chemical Data Sheet' on 'COM-001' in the Appendix for a complete chemical characterization of the active ingredient Metolachlor.

Manufacturing Process

Although specific manufacturing information is withheld, the publicly-available U.S. Patent for the synthesis of Metolachlor shows that it may be produced by reacting the N-substituted aniline above with a chloroacetylating agent, preferably an anhydride or halide of chloroacetic acid. The general process is shown in Figure 1.2 below, which is taken from Vogel and Aebi, U.S. Patent 3,937,730 (1975) and German Patent 2,328,340 (1973).

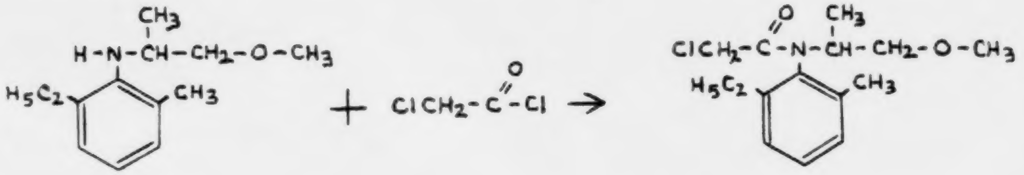


Figure 1.2

Percentages of Components in Pesticide Products

For all pesticide products, the Agency requires a listing of the upper and lower limit established (by the producer or formulator) for each active ingredient, and the upper limit for each impurity or contaminant, reaction product, and degradation product which is known to be present or which might reasonably be identified.

Although the Agency has been supplied with all this information for Technical Metolachlor, the manufacturer has claimed that the identity of impurities or contaminants can indirectly disclose details about the manufacturing process, and that the identity of Metolachlor impurities is therefore Confidential Business Information. The Agency agrees that one can sometimes extrapolate part of the manufacturing process from the identity of impurities or contaminants. The identity of the impurities in Technical Metolachlor is thus not reported in this discussion, but is instead retained by the Agency for internal reference. (Accordingly, in the Appendix, the Chemical Data Sheets for components COM-002 through COM-011 are also withheld from publication.) The Agency does not presently have any reason for concern about the nature of the identified impurities for Technical Metolachlor.

Only the percentage of active ingredient has been supplied for the presently registered formulated end-use products containing Metolachlor.

Technical Metolachlor (manufacturing-use preparations)

1 presently registered: Technical Metolachlor is comprised of minimum 90 to 95 % (by weight) the active ingredient 'Metolachlor', i.e., 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide.

Emulsifiable Concentrate Metolachlor (end-use pesticide)

2 presently registered:
(a) Emulsifiable Concentrate with six pounds of active ingredient per gallon is comprised of 68.5% the active ingredient 'Metolachlor' and 31.5 % inerts.
(b) Emulsifiable Concentrate with eight pounds of active ingredient per gallon is comprised of 86.4% the active ingredient 'Metolachlor' and 13.6 % inerts.

Product Analytical Methods and Data

Methods for detecting and measuring the Metolachlor compound in its registered formulations have been submitted (Helseth and Cole, 1973). Though all the non-Metolachlor components of the Technical product have been identified by its manufacturer (Ciba-Geigy Corporation, 1974), methods have not been reported for determining or measuring any of the impurities in Metolachlor products. This analytical method would only be required if a definite positive response were observed in genetic toxicological tests performed on the Technical. (See the Toxicology chapter for a discussion of genetics effects testing requirements.)

Physical/Chemical Properties

Color: Technical Metolachlor is white to tan. The color of each Emulsifiable Concentrate was not reported.

Odor: Technical Metolachlor is odorless. The odor of each Emulsifiable Concentrate was not reported.

Solubulity: The solubility of Technical Metolachlor was reported to be:
In water - 530 ppm at 20° C
In organic solvents -
Insoluble in 1,2-ethanediol (ethylene glycol)
Insoluble in 1,2-propanediol (propylene glycol)
Miscible with dimethylbenzene (xylene)
Miscible with methylbenzene (toluene)
Miscible with N,N-dimethylformamide
Miscible with 2-methoxyethanol (methyl cellosolve)
Miscible with 2-butoxyethanol (butyl cellosolve)
Miscible with 1,2-dichloroethane (ethylene dichloride)
Miscible with cyclohexanone

Stability: For Technical Metolachlor, the half-life of a 0.25% aqueous solution at 100°C is 30 hours at pH 3, 18 hours at pH 7, and 1.5 hours at pH 10.

Octanol/Water Partition Coefficient: No octanol/water partition coefficient has been reported for Technical Metolachlor.

Physical State: Both Technical and Emulsifiable Concentrate Metolachlor products are in liquid form at room temperature.

Specific Gravity: The specific gravity of Technical Metolachlor is 1.085 (+/- 0.005) at 20°C. The specific gravity of the six pound active ingredient per gallon Emulsifiable Concentrate is 1.04 (+/- 0.005) at 20°C, and the specific gravity of the eight pound per gallon Emulsifiable Concentrate is 1.11 (+/- 0.005) at 20°C.

Boiling Point: At 0.001 mm Hg, the boiling point of Technical Metolachlor is 100°C. For the six pound per gallon Emulsifiable Concentrate (EC), it is 118°C, and for the eight pound per gallon, it is 140 to 160°C.

Vapor Pressure: For the Technical, the vapor pressure is about 10^{-5} mm Hg at 20°C. For the six pound per gallon EC, the vapor pressure was reported to be 0.05 to 1.0 mm Hg at 20°C, and for the eight pound per gallon EC, it was 0.05 mm Hg at 20°C.

pH: The pH of a 10% solution of six pound active ingredient per gallon Emulsifiable Concentrate is between 7 and 8, and that of an eight pound per gallon EC is between 6 and 8.

Storage Stability: Results of ongoing studies show that Technical Metolachlor is stable for a minimum of one year at room temperature. The shelf life of both concentrations of the Emulsifiable Concentrate is estimated to be a minimum of 5 years.

Flammability: No data were available on the flammability of the Technical. The flash point of the six pound per gallon Emulsifiable Concentrate was found to be 118°F (Setaflash C.C.T.), and that of the eight pound per gallon was found to be 185 (+/- 5)°F (TCC).

Oxidizing or Reducing Action: No data were available for the Technical, but the Emulsifable Concentrates were reported to be clearly non-reactive.

Explosiveness: Again no data were available about the Technical. A study on the explosiveness of the six pound per gallon Emulsifiable Concentrate has shown that the material is thermally stable at 200°C, can be processed or handled at temperatures up to 150°C, (under normal use and application practices) does not form (nor does its vapor form) explosive mixtures, and is not shock sensitive. The study on the eight pound per gallon EC is currently in progress.

Miscibility: Both Emulsifiable Concentrate formulations form a stable emulsion with water.

Viscosity: No data were available on the viscosity of the Technical. The six pound per gallon Emulsifiable Concentrate has a viscosity of 15.6 (+/- 0.3) CS at 25°C. The eight pound per gallon, a viscosity of 120 (+/- 5) CD at 25°C.

Corrosion Characteristics: No data were available on the corrosiveness of the Technical. For the Emulsifiable Concentrates, however, it was discovered that the six pound per gallon formulation was not corrosive to steel or tin, while the eight pound per gallon did show a slight corrosiveness.

Dielectric Breakdown Voltage: As long as Metolachlor is not registered for Industrial weed control, it will not be used around high power electrical machinery, and a dielectric breakdown voltage test will not be needed.

DISCIPLINARY REVIEW

Chemistry Profile
Product Specific Data Gaps
Suggested Labeling

Chemistry Profile

The technical material for a pesticide is the toxicant in pure form (usually more than 90 % the active ingredient) as it is manufactured by a chemical company prior to being formulated into an end-use pesticide product. Technical Metolachlor, which is at least 90 to 95 % active ingredient, is an off-white, odorless liquid, soluble in water, and miscible with several organic solvents. Because it is intended only for re-formulation into the end-use pesticide, Technical Metolachlor is a 'manufacturing-use product'. The physical/chemical properties which have so far been determined for the Technical do not suggest any imminent hazards from the handling of the Technical product.

An emulsifiable concentrate is an end-use pesticide product, consisting of a toxicant suspended or dissolved in a water-insoluble organic solvent, stabilized by an emulsifying agent. The strength of an emulsifiable concentrate is usually stated in pounds toxicant per gallon concentrate.

Two strengths of Emulsifiable Concentrate Metolachlor are currently registered: six pounds active ingredient per gallon and eight pounds per gallon. These are somewhat viscous liquids, miscible with water, and having a slightly greater density than water. The physical/chemical properties which have so far been determined for these emulsifiable concentrates indicate a few notable characteristics, due primarily to the presence of the organic solvents: a significant vapor pressure, a relatively low flash point temperature, and a slight corrosiveness to metal containers for the eight pound per gallon. These properties suggest the need for two warnings on the labels of emulsifiable concentrates: due to the vapor pressure and high flammability of the solvent in the six pound per gallon formulation, the user should keep any six pounds or less per gallon formulation away from open flame or high heat; to prevent potential leaks of the eight pound per gallon formulation due to its slight corrosiveness, it should be placed only in application tanks and storage containers that are protectively lined.

Product Specific Data Gaps

The following are "product specific" data gaps for Product Chemistry which need to be filled in order to maintain in effect current registrations under this Standard. After each gap is listed the section in the Proposed Guidelines (July 10, 1978, FR Part 163) which describes that type of data and when it is required.

For Technical Metolachlor:

1)	Octanol/Water Partition Coefficient	163.61-8(c)6
2)	Flammability	163.61-8(c)13
3)	Oxidizing or Reducing Action	163.61-8(c)14
4)	Explosiveness	163.61-8(c)15

5)	Viscosity	163.61-8(c)17
6)	Corrosion Characteristics	163.61-8(c)18
7)	[and, if the Technical is found to produce genetic effects (see Toxicology chapter):] An analytical method (or reference to a method) for detecting and measuring each identifiable impurity (associated with the manufacturing of the technical grade of the active ingredient) in the formulated products of Metolachlor.	163.61-7

For Emulsifiable Concentrate Metolachlor (6 lbs. ai/gallon):

1)	Color	163.61-8(c)1
2)	Odor	163.61-8(c)2

For Emulsifiable Concentrate Metolachlor (8 lbs. ai/gallon):

1)	Color	163.61-8(c)1
2)	Odor	163.61-8(c)2
3)	Explosiveness	163.61-8(c)15

Suggested Labeling

The ingredient statement for Metolachlor products should list the active ingredient 'Metolachlor' as:

"Metolachlor: 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide"

BIBLIOGRAPHY

Each of the following studies contributed useful information to the Agency's review of the product chemistry of Metolachlor, and is considered part of the data base supporting registrations under this Standard.

American National Standards Institute (1976). American National Standard ANSI K62.198-1976. Common name for the pest control chemical 2-chloro-N-(2 methoxy-1-methylethyl) acetamide: "metolachlor". New York, N.Y.

Ciba-Geigy Corporation (1974) Section A, CGA-24705: Name, Chemical Identity and Composition of CGA-24705. (Unpublished study; received Sep 26, 1974 under 100-EUP-44; CDL:96505:A)

Ciba-Geigy Corporation (1975h) Section A, CGA-24705: Name, Chemical Identity, and composition of CAG-24705. Received Nov 25, 1976 under 6G1708. (Unpublished study; CDL:96439-A)

Ciba-Geigy Corporation (1976a) CGA-24705: Name, Chemical Identity, and Composition of CGA-24705. Received Nov 23, 1976 under 100-587. (Unpublished study prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:226955-A)

Ciba-Geigy Corporation (1977) Aerial Application. Received Feb 18, 1977 under 100-583. (Unpublished study that includes studies ID-9D with a summary; CDL:228101-F; 228122)

Ciba-Geigy Corporation (1977ba) Section A General Chemistry. (Unpublished study; received Jan 19, 1977 under 7F1913; CDL:95764-A)

Ciba Geigy Corporation (1977b) Aerial Application. Received Jun 20, 1977. (Unpublished study containing studies ID-10D with a summary; CDL:230672-D, 230683)

Helseth, J.; Cole, G. (1973) The Determination of CGA-24705 in Emulsifiable Concentrates by Gas Liquid Chromatograpy. Method PA-9 dated Nov 14, 1973. Received Sep 26, 1974 under 5G1553. (Unpublished report prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:96666-A)

Vogel, C.; Aebi, R., inventors; Ciba-Geigy Corp., assignee (1976) Plant growth regulating agent. U.S. patent 3,937,730. Feb 10: 8p. Int CI^2. C07G 103.34.

Vogel, C.; Aebi, R., inventors; Ciba-Geigy Corp., assignee (1973) Haloacetanilides acting on plant growth. German patent 2,328, 340. Dec 20: 50p. Int. CI. C07C 103.38.

ENVIRONMENTAL FATE

TOPICAL DISCUSSIONS

Corresponding to each of the Topical Discussions listed below is the number of the section(s) in the 'Proposed Guidelines for Registering Pesticides' of July 10, 1978 (40 FR Part 163) which explain(s) the data that the Agency will need in order to assess Metolachlor's Environmental Fate.

	Guidelines Section
Physico-Chemical Transformation	163.62-7
Soil Metabolism	163.62-8
Microbial Metabolism	163.62-8
Mobility	163.62-9
Spray Drift	163.126-2, -3, and/or -4
Field Dissipation	163.62-10
Accumulation	163.62-11

Physico-Chemical Transformation

Hydrolysis

Metolachlor in buffer pH 5, 7, and 9 at 30°, was respectively 97, 100, and 96% stable for 28 days (Burkhard 1974). From rate constants, Arrhenius parameters for each pH value were calculated. Using the Arrhenius parameters, half-lives for Metolachlor at 20°C were calculated to be greater than 200 days in 0.1N HCl (pH 1) and in buffer pH 5, 7, and 9. In 0.1N NaOH (pH 13), the calculated half-life was 97 days. Hydrolysis of Metolachlor in 0.1N NaOH at 30°C yields N-(2'methoxy-1-methyl-ethyl)-2-ethyl-6-methyl hydroxyacetanilide. In 0.1N HCl at 70°C, Metolachlor hydrolyzed to 4-(2-methyl-6-ethyl-phenyl)-3-methyl-morpholinone-5.

These data were sufficient to show that hydrolysis products are not of environmental concern because Metolachlor is considered to be stable in the natural environment.

Photolysis

Because Metolachlor is used on outdoor crops, studies on photolysis in both soil and water are needed. Because an assessment of re-entry hazard is not required for any of the proposed uses of products containing Metolachlor, a study on photolysis in the vapor phase is not necessary.

Photolysis in Aqueous Solution

Metolachlor was found to be relatively stable in aqueous solution under natural sunlight (Aziz and Kahrs 1975). Approximately 6.6% was photolyzed in 30 days, which was less than 10% of the exposed activity. Five photoproducts, accounting for about 4.7% of the activity, were found in the chloroform soluble fraction. One photoproduct was identified as 4-(2-methyl-6-ethylphenyl)-5-methylmorpholine. Four of the photoproducts were not identified.

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One unknown was found in the aqueous fraction and amounted to about 1.9% of total activity. These photoproducts do not need to be identified because they represent less than 10% of the exposed activity.

Under high intensity artificial sunlight conditions, Metolachlor in aqueous solution was approximately 69% degraded in 15 days (Aziz and Kahrs 1974). Five photoproducts comprising about 13% of total radioactivity were found in the chloroform soluble fraction. Three of the products were identified as 4-(2-methyl-6-ethylphenyl)-5-methylmorpholine (MET-009), N-(2-hydroxyacetyl-N-methoxyprop-2-yl) 2-ethyl-6-methylaniline (MET-001), and N-chloroacetyl-2-ethyl-6-methylaniline (MET-010). (See the Appendix for identities of chemicals referred to by MET numbers.) Photolysis products in the aqueous phase amounted to 23% of the activity. Chloroform soluble products which stayed at the origin on thin layer chromatography (TLC), amounted to 17.2% of the activity. Mass spectroscopy and TLC analyses of this activity indicated that at least five major products were present. Further efforts were taken to separate and identify these products using TLC with a developer of chloroform and methanol (9:1) and chromotropic acid, methanolic sodium hydroxide, and diazonium fluoroborate as specific spray reagents. With this TLC system, at least seven photolysis products were separated. None represented more than 4% of the original ^{14}C activity. These polar products did not contain hydroxyl, aldehyde, or N-hydroxymethyl groups as judged from tests with the specific chromogenic agents.

Based upon the data discussed in this section, Metolachlor is considered to be stable in aqueous solution under natural sunlight.

Photolysis in Soil

Studies on soil slides were performed by Aziz (1974). Under natural sunlight conditions, Metolachlor on soil slides was approximately 50% photolyzed in 8 days. Activity in chloroform extract amounted to 44.9% of the applied radioactivity, of which 32.7% was determined to be parent, 3.9% was identified as N-propen-1-ol-2-yl-N-chloroacetyl-2-methyl-6-ethylaniline, and three unknowns accounted for 7.7%. Each unknown was less than 10% of the applied activity. Non-extractable ^{14}C-activity in soil amounted to 39% of the applied activity. Volatiles accounted for 10.5% of the applied activity, of which 5.2% was determined to be parent.

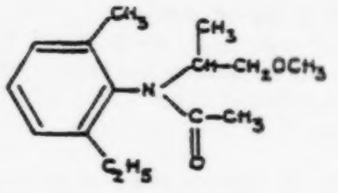
Under artificial sunlight conditions, Metolachlor on soil slides was approximately 52% degraded in 7 days. Activity in the chloroform extract amount to 47.1% of the applied activity, of which 24.1% was determined to be parent, 5.6% was identified as N-propen-1-ol-2-yl-N-chloroacetyl-2-methyl-6-ethylaniline, and 16.4% was comprised of 3 unknowns. (Each unknown was less than 10% of the applied activity.) Nonextractable ^{14}C-residue in soil amounted to 39%. Volatiles accounted for 6.8% of applied activity, of which 4.12% was determined to be parent.

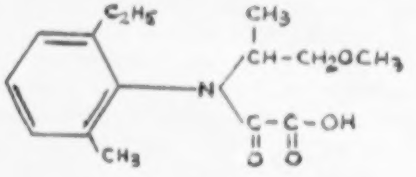
Though either study would have been adequate alone, these studies, the one conducted under natural sunlight and the other under simulated sunlight, provide sufficient information about the photodegradation of Metolachlor in soil.

Soil Metabolism

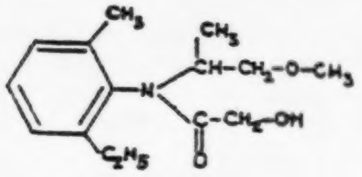
Ellghausen (1976a and b) studied the degradation of Metolachlor in soil under sterile aerobic, nonsterile aerobic, and nonsterile aerobic followed by nonsterile anaerobic conditions. Under sterile aerobic conditions, at the end of 12 weeks, 30% of the reductively dechlorinated analog of Metolachlor (MET-005) was found. No other metabolite could be detected. The remaining radioactivity existed as undegraded Metolachlor.

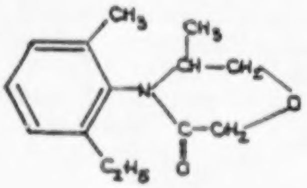
Also at a time interval of 12 weeks, both the aerobic nonsterile and aged aerobic/anaerobic nonsterile tests resulted in a degradation pattern wherein about 18% of the radioactivity was identified as MET-025. Another 10% of the initially applied radioactivity was found as polar, water soluble products. They were inseparable by TLC, but could be methylated with diazomethane to form three distinct components, separable by gas liquid chromatography (GLC). The investigator considers these to be ring hydroxylated analogs of MET-025. A CH_2Cl_2-soluble nonpolar metabolite, representing about 5% of initial radioactivity was compared, by TLC and GLC co-chromatography, to 26 model Metolachlor metabolites with no identity fit. Small amounts of MET-005 as well as unidentifiable polar and nonpolar extractables were also found.


MET-005

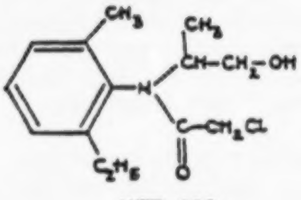

MET-025

Sumner, Szolics, and Cassidy (1976) studied the products of degradation of ring labeled ^{14}C Metolachlor in silt loam treated at an exaggerated rate (100 ppm) and incubated out-of-doors in open bottomed containers. Besides 41.7% of total initial radioactivity found as Metolachlor, 0.9% of MET-001 and 0.1% MET-008 were found. Additionally, an oxalic acid derivative was tentatively identified as MET-025. Chemicals contained in the leachate from this study were qualitatively similar, as determined by comparative radioassay of various TLC R_f zones.

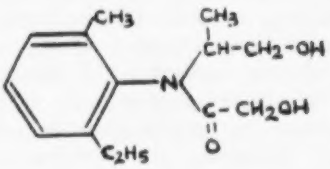

MET-001


MET-008

Concurrently, Sumner, Szolics, and Cassidy (1976) conducted a field plot study of silt loam soil treated at 2 lbs active ingredient per acre (a.i./A) and aged 12 months. This study yielded in addition to MET-001, MET-008, and MET-025, the additional compounds MET-003 and MET-026.



MET-003



MET-026

All metabolites in both substudies were less than 1% of total radioactivity, except MET-001 in the leachate, which represented 2.5% of total radioactivity. Two TLC spots, representing metabolites less polar than MET-003 were also noted, both at the 1% level, in the extracts from the field experiment; the two spots as well as a spot near the TLC plate origin represented 6.4% of the total radioactivity.

Sumner and Cassidy (1975a) showed that under field conditions, over a one year period, the relative percentage of unextractable residues reached a steady state (ca. 80% of total). During the latter stages of the test, the relative amount of extractable residue in the organic fulvic and humic acid fractions decreased with a concomitant increase in the amount remaining in H_2O soluble and mineral fractions. The fractionation procedure used was described by Sumner (1974).

Dupre (1974a) conducted an anaerobic soil metabolism study as described in the Agency's Proposed Guidelines for testing and found that the gross character (extractable polar, extractable nonpolar, or nonextractable) of soil metabolites did not change over a 60-day anaerobic period following a 30-day pre-conditioning aerobic period, as compared to the character of degradates during a similar period of continued aerobic metabolism.

Evidence is provided by Sumner and Cassidy (1975a) that nonextractable bound residues of Metolachlor and its metabolites are in dynamic equilibrium with soluble forms and that the nonextractable portion may therefore serve as a long term reservoir for extractable residues.

When viewed as a composite, these tests satisfy the soil metabolism data requirement for Metolachlor. (The following additional studies contain information related to metabolic transformation in soil but did not by themselves supply adequate information about soil metabolism: Kaiser 1974, Sumner and Cassidy 1974g, k, l, m, f, and e).

Microbial Metabolism

Three microbial metobolism studies were available. One was conducted according to the alternative pure or mixed culture technique and two were conducted by the sterile and non-sterile soil approach.

In the pure and mixed culture study (McGahen and Tiedje), American Type Culture Collection number 34507, identified as Chaetomium globosum, a soil fungus, was used in resting cell experimentation at 0.035 mM concentrations of Metolachlor including control flasks without Metolachlor and without C. globosum. Control flasks did not exhibit any degradation for 144 hours. Flasks with C. globosum and Metolachlor exhibited substantial degradation with only 55% of Metolachlor remaining after 5-7 days. An adaptive lag period of approximately 20 hours was observed. A total of at least eight extractable products were identified or tentatively identified.

MET-009, MET-003, MET-018 and MET-019 were firmly identified. Identifications of MET-020, MET-021, MET-022, MET-023, and MET-024 were tentative. The formation of the oxoquinoline is unique to pesticide metabolism, with the three quinolines of Metolachlor unique to Metolachlor itself. It is apparent that the fungus did not remove any group from the ring, although it dehydrogenated the ethyl moiety to form a vinyl on the ring.

Kaiser, using labeled Metolachlor (position of label unspecified) added Metolachlor to both sterilized and unsterilized sandy loam soil at a concentration of 10 mg/250 gm of soil (40 ppm) (Kaiser, 1974). Essentially no loss of total activity was noted in either sterile or non-sterile soil (5-15% of the residual activity was found to be degradation products of Metolachlor). This study is not considered acceptable for the purpose of describing the effects.

In another sterile and non-sterile soil study (Ellgehausen, 1976b,c), a clay loam (Stein, Switzerland) which was treated with ring-labeled Metolachlor at a concentration of 1 mg/232 gm of soil (ca. 4 ppm) and a control sample (autoclaved soil) were monitored for degradation. After a short lag phase, a slow but steady evolution of $^{14}CO_2$ was evolved in the non-sterile soil reaching 4.8% of the applied dose after 12 weeks. Analysis of the soils after 12 weeks indicated that 10% of the residual activity in the non-sterile soil was parent compound versus 65% Metolachlor in the sterile soil.

On the basis of these studies, a general microbial transformation scheme can be postulated which involves dehalogenation, dehydrogenation, dealkylation, ring formation, and oxidation of the acetyl group and/or ring oxidation. Ring oxidation apparently results after extended incubation of the compound in the presence of microbes, but it is not a significant route of degradation.

The studies by McGahen and Tiedje and by Ellgehausen followed acceptable protocols, and are sufficient to support this facet of the fate assessment for the present uses of Metolachlor.

Mobility

Leaching

Data on leaching have been developed by Dupre (1974c) and Houseworth (1973b). Parent Metolachlor leaches readily in sandy loam and sandy soils low in organic matter. Twenty to 33% of the applied Metolachlor leaches more than 12 inches in the above soils when an equivalent of 20 inches of rainfall are applied to a soil column overlayered with Metolachlor. Conversely, insignificant leaching is expected in muck soils high in organic matter. Field studies (Ballantine, 1975) showed substantial leaching into the 6"-12" soil horizon in 5 different states with various soil types. Metolachlor residues, aerobically aged for 30 days in soil, will also leach in soils low in organic matter. These data are sufficient to assess leaching potential for Metolachlor.

Adsorption

A laboratory adsorption/desorption study using four concentrations of radiolabeled or non-radiolabeled pesticides and the same soil as used for the leaching study is not presently available for Metolachlor. This constitutes a data gap.

Spray Drift

Information on the likelihood or extent of spray drift for Emulsifiable Concentrate Metolachlor when conventional ground sprayers are used is not presently available, except for what is generally understood about the spray drift behavior of similar agricultural chemical preparations. Subpart J of the Proposed Guidelines, which will cover drift as it relates to phytotoxic effects, has not yet been accepted for regulatory use. Because Metolachlor is a herbicide which may potentially damage an adjacent crop or neighboring flora, when these Guidelines do go into effect, drift studies may be required.

Field Dissipation

Field dissipation studies were conducted by Ballantine (1975) on five different soil types representing five geographical locations. The following conclusions were drawn from the studies: 1) Approximately 10% of applied Metolachlor was found in the upper 12 inches of Mississippi loam after 60 days for both 2 and 4 lbs. active ingredient per acre (a.i./A) application rates. 2) In Nebraska silt loam, approximately 10% of applied Metolachlor was found in the upper 12 inches after 162 days for both 2 and 4 lbs. a.i./A application rates. 3) In New York, California, and Illinois, soils that were not analytically characterized, Metolachlor dissipated to about 10% of the applied in 60 to 150 days for both 2 and 4 lbs. a.i./A application rates.

These field dissipation studies under actual use conditions are sufficient to show that Metolachlor, applied alone, dissipates to approximately 10% of the applied amount in 60 to 160 days in each soil type tested, and that it leaches to approximately 12 inches in loam and silky loam soils. If uses were proposed at greater than 4.0 pounds ai/A pre-emergent, then additional field dissipation tests, at the proposed rates, would be needed.

Accumulation

Rotational Crops

Oats in the greenhouse, and carrots and soybeans in the field, were grown as rotational crops to corn 9 months after soil treatment at 2 lbs/acre using ^{14}C-ring labeled Metolachlor. Low levels of residues ranging from 0.02 to 0.27 ppm, expressed as Metolachlor, were found in different portions of the various crops (Sumner and Cassidy 1974e; Sumner and Cassidy 1974f; Sumner and Cassidy 1974g). The preponderance of extractable residues were polar in nature (partition into H_2O/MeOH vs. $CHCl_3$) and the two major fractions constituting these polar residues were neutral and acidic in nature, as determined by ion exchange chromatography. A typical analysis of such plant residues is provided by the following example for oat straw derived from oats grown as a rotational crop to corn where Metolachlor was applied at a rate of 2 lbs/acre (Sumner and Cassidy, 1974f).

		Calculated ppm as Metolachlor
1) Total ^{14}C activity	= 0.27 ppm	
2) H_2O/MeOH extractable, % of total activity	= 67%	.18
- Neutral Fraction, % of total activity	= 19%	.05
- Acidic Fraction, % of total activity	= 45%	.12
3) $CHCl_3$ extractable, % of total activity	= 7.0%	.02

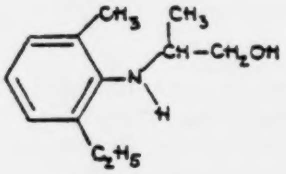
The text of the review by Marco (1974) of metabolism studies with Metolachlor in corn implies that only highly polar acid metabolites, such as conjugates involving the N-acetyl group of Metolachlor are present. However, the data presented in Table IV of Marco (1974) show that the relative amounts of polar neutral and polar acidic constituents in extracts of mature stalks differ by about 4 to 1. These data support the contention that TLC characterization of the polar neutral constituents should be possible. Sumner and Cassidy (1974d) did not adequately characterize the polar neutral constituents, though the very low levels of radioactive content in these fractions made further characterization difficult by means of present-day technology.

(Adapted From Table IV, Marco-1974)
Ionic Characterization of Radioactive Metabolites in Polar Fraction of Corn Treated with 2 lb. ai/A ^{14}C Metolachlor

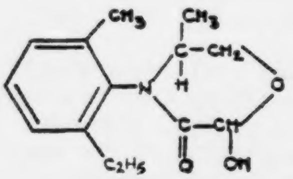
Location	Ionic Charge	Percent of Total ^{14}C in Plant			
weeks after treatment		8	12	16 (mature forage)	
Greenhouse	Neutral	7.0	7.9	a	(a = sample decomposed in shipment)
	Acid	73.1	53.6	a	
	Base	0.6	0.9	a	
	Zwitterion	6.2	21.4	a	
Field	Neutral	7.4	10.8	7.3	
	Acid	68.2	70.4	26.3	
	Base	1.7	1.2	1.0	
	Zwitterion	2.7	8.4	15.3	

Marco (1975), and Sumner and Cassidy (1975), argue that the metabolic pathways in rotational carrots and soybeans are qualitatively similar based on a comparison of the ionic and TLC comparative characteristics of acidic constitutents. While it is conceded the conjugated metabolites of Metolachlor in corn grain may be the only ones worthy of consideration, the same is not necessarily true with rotational crop uptake. Compounds unable to readily form sugar and/or S-glutathione conjugates may be taken up by rotational crops and exist as discrete residues. These may therefore be worthy of individual consideration by the toxicologists.

Also, it should be noted that the official regulatory method for Metolachlor and its metabolites in corn is based on an acid hydrolysis which forms HP-001 and HP-002. (Aziz and Ross, 1975).



HP-001



HP-002

This method will not detect MET 002, 004, 008, 009, or 010, all of which are postulated degradation products of Metolachlor (Marco, 1974), and none of which can readily form the conjugates, but could form oxo-neutral conjugates. Again, using the oat (straw) example, cited above, one can conclude that the entire neutral fraction of the H_2O/MeOH extractables equaling 0.05 ppm could be a mixture of MET 002, 004, 008, 009, and 010 (or other degradates of a similar nature) and would not be detectable by the method of Balasubramanian, Aziz, and Ross (1975). Such compounds should be readily amendable to GLC and TLC separation R_f zone and retention time comparisons with model compounds.

Based on information submitted by Ballantine (1975), the roots of root crops, grain of small grains, and oil from oil seed crops (such as cotton seed) can reasonably be expected to contain little, if any, residue of Metolachlor per se or its metabolites hydrolyzable to HP-001 or HP-002 using the method of Balasubramanian, Aziz, and Ross (1975). All residue analyses for MET-007 were 0.03 ppm or less and were 0.10 ppm or less for MET-015. The question as to whether this regulatory method for corn-related products is applicable to rotational crops is moot and must await further elucidation of the nature of the neutral polar metabolites in rotational crops.

The studies cited above show that levels of Metolachlor-derived residues in other plant portions of these crops (carrot tops, soybean stalks, sugar beet tops, and wheat straw) may at times be expected to exceed this analytical "baseline" level when grown as rotational crops to corn and analyzed by the procedure of Balasubramanian, Aziz, and Ross, 1975.

Lettuce was grown outdors as a rotational crop to soybeans in the fall and spring, 14 and 41 weeks respectively, after soil was treated at 2 lbs. a.i./acre with ^{14}C-ring labeled Metolachlor. The residue level, expressed as Metolachlor, found in the 26-week old fall planting of lettuce, was 0.025 ppm. The levels observed in the second crop (spring planting) were 0.144 ppm in the 13-week old sample and 0.062 ppm in the 15-week old sample (final harvest).

Only the 54-week lettuce sample (second crop, spring sample) was considered to contain a sufficiently high level of residues for further characterization, which consisted of partitioning the radioactivity into organic, polar, and non-extractable fractions. The fractions contained 21%, 73%, and 12% of the activity, respectively. No further identification was attempted.

The data on rotational crop residues are deficient in two respects: first, acceptable data are not available on residues in small grains, root crops, or leafy vegetables to establish an interval between Metolachlor treatment and the planting of rotational crops so that carry-over residues into rotational crops are prevented; second, although it is agreed that present day analytical technology is not easily adapted to the task, the extractable non-polar metabolites in rotational crops were not sufficiently characterized to dispel concern over their potential contamination of the food web.

The registered rotational crops restriction provides that: "Small grains may be planted 4-1/2 months following treatment. Field corn (except fresh corn and popcorn), cotton, soybeans, peanuts, sorghum, root crops, and small grains may be planted in the spring following treatment. Do not graze or feed forage or fodder from cotton or small grains to livestock. All other rotational crops may be planted 18 months after application."

However, the Agency has a new policy on rotational crops: EPA will now accept petitions for 'rotational crop tolerances' for rotated crops, and where necessary, for meat, milk, and eggs. When the rotational crop restrictions that would ensure the absence of residues in rotated crops are not practical for the grower, tolerances may be set for residues in specific rotated crops, and an earlier planting of those rotated crops may be allowed. In brief, the registrant now has the option, for each rotated crop, of: (1) accepting a crop rotation restriction interval (not to exceed 18 months) which is sufficient to ensure that residues are not present in the rotated crop; or (2) petitioning for a 'rotational crop tolerance' for that crop, which may allow for an earlier rotation.

Studies in which Metolachlor was applied in accord with existing usage showed residues, and the need for tolerances for these residues, in the forage and fodder of small grains, in the tops of sugar beets and carrots, and in lettuce. Under the new policy, because there is no 'rotational crop tolerance' for residues in the forage and fodder of small grains, for residues in the tops of sugar beets and carrots, or for residues in rotated lettuce (or other leafy vegetables), crops in these crop groupings should not be rotated in Metolachlor-treated fields before 18 months. Cotton for cottonseed would be an exception to this restriction, because the data for rotational soybeans showed that the mature soybean contained either non-detectable or very small amounts of Metolachlor residues. Higher levels were found in soybeans foliage. Therefore it may be extrapolated that cotton foliage, but not cottonseed, will contain detectable levels of residues when cotton is grown as a rotational crop in the spring following the treatment of corn, soybeans, peanuts, or sorghum with Metolachlor. Because cotton foliage would be expected to contain residues of Metolachlor, it should not be fed to livestock.

Thus, unless additional data are submitted to demonstrate intervals (less than 18 months) after which no residues will occur in rotational crops, or unless tolerances are established for those rotated crops which would contain residues, the label on any product formulated with Metolachlor and intended for use on food or feed should carry the following rotational crops restrictions: "Field corn (grown for grain, except popcorn), cotton, soybeans, peanuts, and grain sorghum may be planted in the spring following treatment. Do not rotate other crops until 18 months after application. Do not graze or feed forage or fodder from cotton to livestock." In the meantime, in accordance with the conditional registration policy authorized by Section 3(c)(7) of FIFRA and implemented under 40 CFR 162.18, this Standard will retain the existing rotational crop restrictions and simply state the data requirement for additional rotational crop data for small grains, root crops, and leafy vegetables.

Fish Accumulation

Ellegĥausen (1977) tested the uptake, transfer and degradation of Metolachlor by algae, daphnia, and catfish. After 90 minutes exposure to 0.1 ppm Metolachlor, algae accumulated 10.4 ppm. However, following 2 hours depuration, less than 2 ppm remained in the cells. Daphnia, exposed for 24 hours to 0.1 ppm, accumulated 0.60 ppm. Eight hours depuration was needed to achieve a 50% loss. Daphnids accumulated only 20% more when exposed to both algae with 10.4 ppm Metolachlor and water containing 0.1 ppm Metolachlor as compared to fortified water in the absence of algae. Catfish, exposed to 0.1 ppm ^{14}C Metolachlor accumulated 1.20 ppm Metolachlor in their tissues after 96 hours. However, a plateau was not reached.

Metabolites of Metolachlor were noted but not identified in the algae, daphnids, and catfish. At the end of the 96-hour catfish study, only 1/2 of the ^{14}C-activity remaining in the water was Metolachlor. The remainder was present as 3 unidentified degradation products. The theoretical basis for the model system used was discussed in another paper

(Elleghausen, 1976b). Smith (1977) conducted a 30-day catfish exposure study in a soil/water/fish ecosystem. At an average concentration of 0.08 ppm in the water, bioaccumulation factors were 6.5 - 9.0 for edible portions of the fish and 55.0 - 92.4 in the viscera. After 14 days of withdrawal, residue levels in the edible portion declined from a maximum exposure value of 0.72 ppm to 0.03 ppm, and levels in the viscera declined from a maximum exposure value of 7.39 ppm to 0.18 ppm. The accumulated residues in the edible portions remained relatively constant in terms of extractable vs. nonextractable (about 8:1). On days 1 and 30 there was 16 times more organically soluble activity than aqueous soluble (ethyl acetate-water system). A cysteine conjugate of Metolachlor was identified as a metabolite and reached a high of 12.8% of total ^{14}C activity in the edible tissue on day 14. Smaller amounts of other metabolites were found in edible and/or visceral tissues but were not identified.

N-(2'hydroxy-1'-methylethyl)-2-ethyl-6-methyl chloroacetanilide (MET-003), N-2(2-hydroxy acetyl)-N-(1-methyl propane-2-yl)-2-ethyl-6-methyl aniline, and a cysteine metabolite of Metolachlor were all found in water along with three other unidentified degradation products.

Barrows (1974) reported on a bluegill sunfish flow-through study at ^{14}C Metolachlor exposure levels of 10 and 1000 ug/liter. Bioaccumulation levels at the 1000 ug/liter exposure level reached 28 ppm in edible tissues and 702 ppm in the nonedible tissues. Existence of a plateau could not be established. After 28 days depuration, residues in edible portions of fish decreased to 0.08 ppm for the 10 ug/liter ^{14}C Metolachlor exposure and to 11.7 ppm for the 1000 ug/liter exposure. The chemical nature of the fish residues was not defined. When the above studies are considered as a composite, they are sufficient to adequately characterize the fish accumulation characteristics of Metolachlor.

DISCIPLINARY REVIEW

Environmental Fate Profile
Exposure Profile
Generic Data Gaps
Suggested Labeling

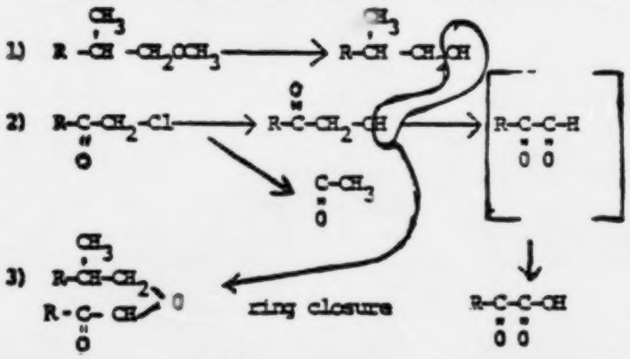
Environmental Fate Profile

Metolachlor is applied at a rate of 1.5 to 3.0 pounds active ingredient per acre to soil where corn (excluding popcorn), soybeans, peanuts, or grain sorghum are to be grown. Normally, the chemical is sprayed on the soil during or soon after planting, before sprouts emerge. However, when dry weather is expected, or if furrow irrigation is being used, the chemical is sprayed on the soil before planting, and incorporated into the top 2 inches of soil.

Metolachlor is quite stable to hydrolysis over the environmental pH range of 5 to 9 (the estimated half-life is 200 days over this entire pH range). Photolysis appears to be a more significant degradation pathway, as approximately 50% was found to have degraded on sunlit soil over a period of eight days. However, if Metolachlor is applied and incorporated into the top 2 inches of soil, then degradation by photolysis is expected to be minimal. Soil metabolism, by both aerobic and anaerobic microorganisms, would also play an important role in the degradation of Metolachlor in the soil (McGahen and Tiedge, 1978).

About 30% of the photoproducts were represented by MET-009 and MET-001. (See the Chemical Fact Sheets in Appendix A for characterizations of these and other metabolites.) Another 30% was represented by $CHCl_3$ and water-soluble polar metabolites. Indirect evidence obtained from analysis of aqueous photoproducts produced by artificial light of <280 nm suggests that the polar products, both aqueous soluble and $CHCl_3$ soluble, are not aldehydes or phenolic in nature (Aziz and Kahrs, 1975). Exposure of ^{14}C Metolachlor treated soil thin layers to natural sunlight (Aziz, 1974) resulted in gradual photolysis to MET-003 and three unidentified products. Two unidentified products have moderate polarity and one was relatively high in polarity. After 8 days exposure, about 1/2 of the initially applied dose had decomposed.

Soil metabolism of Metolachlor appears to proceed by hydrolytic cleavage of the N-alkyl terminal constituents followed by oxidation and/or ring closure. The following reactions were found to occur on the N-alky groups:



(Elleghausen, 1976a and 1976b; Sumner, Szolics, and Cassidy 1976; Sumner and Cassidy, 1974 and 1975)

Attack of the benzenoid portion of the molecule to form phenolic metabolites was speculated but not proven (Elleghausen, 1976b). The likelihood of such ring attack is contraindicated by the following observations: (1) Evidence is provided by Sumner and Cassidy (1974) that non-extractable bound residues of Metolachlor are in dynamic equilibrium with soluble forms, (2) unextractable residues represented by fulvic and humic acid fractions decrease with increased aging. Incorporation of polyphenolic metabolites into the soil organic matrix would mitigate against both of the above findings.

Studies were also available on Metolachlor's environmental mobility. Houseworth (1973b), in a laboratory column leaching study, using a wide range of soil types, showed that Metolachlor per se is subject to extensive leaching when applied to soils having low organic content. Extensive leaching can thus be expected in soils such as agricultural sands and sandy loams having organic contents of 2% or less. Residues of aged ^{14}C-Metolachlor were also found to leach extensively in sandy loam soil (Dupre, 1974). Based on incremental ^{14}C activity at different soil depths, several discrete chemicals of different mobilities were probably involved. A runoff study by Dupre (1974c) showed that Metolachlor can be expected to move from agricultural sites of application both by sheet erosion and leaching.

Field dissipations studies confirmed Metolachlor's potential for significant movement in the soil, but left open the question of whether Metolachlor may sometimes persist undegraded. Skipper, Gossett, and Smith (1976), in field dissipation tests, concluded that extensive leaching was the major cause of dissipation from the upper 3-inch soil horizon in two different plots containing sandy loam soils. Field dissipation studies of Metolachlor applied at up to 4 lbs. a.i./acre (pre-emergent) showed residues generally less than 10% of the amount originally applied over time spans ranging between 107 and 162 days. A total of 5 states representing continental USA climate extremes were involved. But absolute losses of Metolachlor between the day of application and final sampling were not always so great. For example, in a Nebraska study, residues declined only 44% over a 107-day time span. In some cases, substantial residues were found in the 6" to 12" soil horizon suggesting extensive leaching. This high soil mobility, in combination with a potential for long-term environmental stability, may prove to be significant concern in projecting potential exposures to Metolachlor residues.

Additional studies were performed to estimate the possibility of Metolachlor bioaccumulation. Bluegill sunfish exposed for 70 days to a mean level of 1.2 ppm ^{14}C Metolachlor accumulated 18 ppm of ^{14}C activity (expressed as Metolachlor) in their edible tissues and 486 ppm in non-edible tissues. After a 28-day depuration, the residue levels decreased to 12 and 13 ppm respectively. The chemical nature of the residues was not investigated (Barrows, 1974). A catfish study (Smith, 1977) involving aged Metolachlor on sandy loam soil resulted in an accumulation of 0.53 ppm in edible catfish tissue at the end of 30-day exposure. After 14 days of depuration, the level decreased to 0.03 ppm. Values for viscera at the end of the 30 day exposure and after 14 days depuration were 4.4 and 0.18 ppm, respectively. The major identified metabolite found in the edible tissues was CGA-46576.

Though the available data do not indicate significant long-term accumulation in fish, there is a possibility that residues may result in rotated crops grown on Metolachlor-treated soil. Roots of root crops, grain of small grains, and oil from oil seed crops, grown as rotational crops to corn in a Metolachlor-treated field, were shown to have little, if any, residues of Metolachlor, as analyzed by the officially accepted regulatory method for corn grain, forage, and fodder (Balasubramanian, Aziz, and Ross 1975; Ballantine 1975). This method will detect Metolachlor per se and a series of sugar and glutathione conjugates which can form after hydrolysis of the N-alkyl groups of Metolachlor to terminal OH groups. ^{14}C studies on rotational crops to corn, however, gave evidence of other possible metabolites which, if present in a rotational crop, would not be detected by the official regulatory method for corn products. Also, the following types of rotational crop products were found to contain finite residues in one or more samples collected for analysis by the method of Balasubramanian, Aziz, and Ross (1975): carrot tops, soybean stalks, sugar beet tops, and wheat straw. Finally, lettuce rotated on a soybean plot treated with ^{14}C-Metolachlor contained detectable residues in samples of spring and fall seedlings, 41 and 56 weeks after treatment, respectively (Newby, 1979).

Exposure Profile

Technical Metolachlor: For persons involved in the handling, storage, or shipment of Technical Metolachlor, there is little likelihood of oral exposure, and because of the low vapor pressure of the viscous liquid, there is also little chance of inhalation exposure. The most likely human exposure is a repeated dermal exposure, and occasionally, by accident, an occular exposure.

The fate data have indicated the relative stability of Metolachlor to hydrolysis and metabolic degradation, and its high mobility in the terrestrial environment. Thus, for wildlife in the proximity of Technical Metolachlor manufacture, storage, shipping, or disposal, if significant amounts of the chemical were spilled, drained, discharged, or disposed of in the natural environment, it is possible that exposure could occur to various species, but particularly aquatic species, and perhaps to carnivores feeding on contaminated fish. Also, considering Metolachlor's potential for rotational crop uptake, plants growing on contaminated soil could pass on residues to herbivores, including birds.

Emulsifiable Concentrate Metolachlor: Though all pesticide products, but particularly those mixed with seed or foodstock before application, present some possibility of accidental ingestion, for persons involved in the dilution, mixing, and application of Metolachlor formulations, there is little chance of oral exposure. But there is a significant possibility of dermal and eye exposure from the splashing that may occur in diluting and tank mixing, and in the loading of spray equipment. The vapors from the Emulsifiable Concentrates are limited by the vapor pressure and the viscosity of the solutions, thus limiting the chance of inhalation exposure during mixing or loading. But the spray droplets generated by the application of end-use Metolachlor may result in an inhalation and/or dermal exposure for applicators and for agricultural workers or livestock who may be in direct proximity to the spraying.

As concerns the possibility of wildlife exposures from Metolachlor's end-uses, several aspects of Metolachlor's fate combine to suggest that Metolachlor may have a potential to contaminate natural freshwater habitats. This suspicion is supported by the following test findings: laboratory column leaching studies, using a wide range of soil types, show that Metolachlor *per se* is subject to extensive leaching when applied to soils having a low organic content; field tests designed to show dissipation and mobility concluded that extensive leaching was the major cause of dissipation in soil, with residues found to a depth of 12 inches below the surface; runoff studies showed that Metolachlor can move from agricultural sites of application both by sheet erosion and leaching;

Metolachlor is stable to hydrolysis over the environmental pH range of 5 to 9; the estimated half-life for Metolachlor in water is over 200 days; loss due to photolysis is minimal (6% over one month); and Metolachlor can be resistant to microbial degradation, with soil half-lives reported to be greater than 107 days, and anaerobic degradation rates observed to be slower and even non-existent. It is thus concluded that Metolachlor's end-uses may have the potential to contaminate groundwater via leaching and possibly by surface contamination (at the well head), thereby exposing freshwater fish and other freshwater plants and animals, animals which drink the contaminated water, or carnivores which feed on contaminated fish. Also, because of Metolachlor's demonstrated uptake by rotational crops, it may be assumed that some aquatic or terrestrial plants may either suffer phytotoxic exposures or pass Metolachlor residues on to herbivores, including birds.

Because there is a concern that residues may migrate to and persist in aquatic habitats, there is a need to quantitatively determine potential aquatic exposures, so that these potential exposures can be compared with toxic levels for sensitive species. For this purpose, the Agency will require that residue monitoring be performed after actual applications at several sites selected for their ability to demonstrate the potential for aquatic contamination. The Agency has identified, in a three-step process of selection, two watersheds which have been determined appropriate for Metolachlor field monitoring: first, the Agency identified the regions of the United States in which the most corn, soybeans, peanuts, and grain sorghum are grown; secondly, the Agency found six watersheds within these potential Metolachlor use regions which have terrain and soil types that could promote the contamination of freshwater by leaching or runoff (i.e., a relatively low organic content and flat terrain for leaching, and a high organic content and hilly terrain for runoff) (Radtke, 1980); finally, the Agency selected the two watersheds which provided the best delimitation of variables to allow for the clearest interpretation of results. The two sites which the Agency thereby selected as appropriate for watershed residue monitoring are: one watershed just south of Treynor in Pottawattamie County, Iowa; and the Little River experimental watershed near Tifton, Georgia.

The possibility for Metolachlor residues to occur in food or feed, which may result in dietary exposures to humans, livestock, or domestic animals, is discussed in the 'Residue Chemistry' chapter.

Generic Data Gaps

The following are gaps in the Environmental Fate data base which will be used to support registrations under this Metolachlor Standard. Opposite each gap is given the section in the Proposed Guidelines of July 10, 1978 (FR Part 163) which describes that type of data and when it is required.

1) Adsorption/desorption studies	163.62-9
2) Accumulation studies on rotational crops for small grains, root crops, and leafy vegetables.	163.61-11(b)
3) Actual field residue monitoring studies at two watershed sites to be approved by the Agency.	(no guidelines)

Suggested Labeling

There are no environmental fate labeling requirements for manufacturing-use Metolachlor labels.

Conditional upon the registrant's agreement to provide the supporting rotational crops data, Emulsifiable Concentrate Metolachlor should carry the following rotational crops restriction on its label:

> "Small grains may be planted 4-1/2 months following treatment. Field corn (except fresh corn and popcorn), cotton, soybeans, peanuts, sorghum, root crops, and small grains may be planted in the spring following treatment. Do not graze or feed forage or fodder from cotton or small grains to livestock. All other rotational crops may be planted 18 months after application."

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TOXICOLOGY

TOPICAL DISCUSSIONS

Corresponding to each of the Topical Discussions listed below is the number of the section(s) in the 'Proposed Guidelines' of August 22, 1978 (FR Part 163) which explain(s) the data that the Agency will need in order to assess Metolachlor's Toxicology.

	Guidelines Section(s)
Metabolism and Pharmacodynamics	163.85-1
Acute Effects and Neurotoxicity	163.81-1, -2, -3, and -7
Local Irritation	163.81-4 and 163.81-5
Subchronic Effects and Neurotoxicity	163.82-1, -2, -4, -5, and -6
Sensitization	163.81-6
Chronic Effects	163.83-1
Oncogenicity	163.83-2
Mutagenicity	163.84-2, -3, and -4
Teratology	163.83-3
Reproductive Effects	163.83-4

Metabolism and Pharmacodynamics

Metabolism studies on Metolachlor (Hambock, 1974a,b) demonstrated that:

(a) Most orally administered Metolachlor is rapidly absorbed, metabolized, and excreted.

(b) The urine and feces of treated animals contained a complex pattern of metabolites; each metabolite accounted for less than 5% of the administered dose. No unchanged drug was detected in urine or feces samples.

(c) Approximately half the urinary and fecal radioactivity was extractable with organic solvents.

(d) No glucuronide or sulfate conjugates were found in the excreta.

(e) Several excreted metabolites were tentatively identified and appear to result from dechlorination, O-methylation, N-dealkylation, and side chain oxidation in the rat.

In an additional study (Hambock, 1974c), male rats were treated with ^{14}C Metolachlor (approximately 31 mg/kg, p.o.), and urine and feces were collected for 48 hours. The urine and feces contained 21.5% and 51.4% of the administered dose, respectively, and the halflife was determined to be approximately 28 hours. TLC, GLC, HVE (high voltage electrophoresis), column chromatography, gel permeation chromatography, and enzymatic hydrolysis were adequately utilized to identify radioactive metabolites, which were identified as 2-ethyl-6-methylhydroxyacetanilide (MET-002) and N-(2-ethyl-6-methylphenyl)-N-(hydroxyacetyl)-DL-alanine (MET-004) in the urine and 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methylethyl)acetamide (MET-003) and MET-004 in the feces. The 48 hour excreta contained 1, 15, and 22% of the administered dose as MET-002, MET-004, and MET-003 respectively. (See the Appendix for Chemical Data Sheets on MET-002, MET-003, and MET-004.)

These studies demonstrate the relatively rapid metabolism and excretion of Metolachlor, and are sufficient to fulfill the requirement for this type of information.

Acute Effects and Neurotoxicity

Acute Oral Toxicity

The minimum testing needed on acute oral toxicity is one test on the laboratory rat for each technical and formulation.

For Technical Metolachlor, the acute oral LD-50 in the laboratory rat is 2,780 mg/kg with 95% confidence limits of 2,180-3,545 mg/kg (Bathe 1973). Technical Metolachlor in corn oil has been shown to be emetic in beagle dogs to an extent that precludes the establishment of an oral LD-50 in dogs (Affiliated Medical Research, Incorporated, 1974e). The study did, however, establish the 'emetic dose 50' to be 19.0 (+/- 9.7) mg/kg. The Technical therefore falls into Category III with regard to acute oral toxicity.

Tests were also done on the two Emulsifiable Concentrate formulations. In a test involving a 6-pound per gallon E.C. formulation, the acute oral LD-50 was found to be more than 2,000 mg/kg but less than 5,000 mg/kg in the rat (Affiliated Medical Research, Incorporated, 1974d). In a test involving an 8-pound per gallon E.C. formulation, the acute oral LD-50 in the laboratory rat was 2,530 mg/kg with 95% confidence limits of 1,890-3,400 mg/kg (Nham and Harrison, 1977a). A related study (Affiliated Medical Research, Incorporated, 1974f) established that the 'emetic dose 50' in dogs to a 6-pound per gallon E.C. was 24.5 (+/- 9.2) mg/kg. Based on the above data, it is anticipated that E.C. formulations of Metolachlor as high as 8-pounds per gallon can be expected to produce an oral LD-50 of not less than approximately 1,890 mg/kg in the rat. The available data, then, places both existing E.C. formulations in Category III with regard to acute oral toxicity.

Acute Dermal Toxicity

The minimum testing needed on acute dermal toxicity is one test, preferably on the albino rabbit, for each technical and formulation.

Affiliated Medical Research, Incorporated (1974a) established that the LD-50 of the Technical to the New Zealand rabbit is greater than 10,000 mg/kg when tested by the unabraded dermal route. The above information is sufficient to meet the requirement for acute dermal toxicity data on intact skin. The unabraded dermal test results place the Technical in Category III with respect to acute dermal toxicity.

In a test involving a 6-pound per gallon E.C. formulation, the acute dermal LD-50 to the New Zealand rabbit was found to be greater than 10,000 mg/kg by the intact dermal route (Affiliated Medical Research Incorporated, 1974b). For an 8-pound per gallon E.C. formulation, it was established that the acute dermal LD-50 to the New Zealand rabbit is greater than 3,038 mg/kg via the intact dermal route (Nham and Harrison 1977b). A related study (Tryzna and Paa, 1976) determined that the acute dermal LD-50 of a 1 to 10 dilution of a 6-pound per gallon E.C. formulation was greater than 16,000 mg/kg via the intact dermal route. The available data, then, places both existing E.C. formulations in Category III with respect to acute dermal toxicity.

Acute Inhalation Toxicity

The minimum data needed on acute inhalation toxicity is one inhalation LC-50 test, using one mammalian species, preferably the albino rat, for each technical and formulation.

Acute inhalation toxicity for the Technical was tested by Sachsse and Ullman (1974a). In that test there were no deaths in albino rats at the maximum achievable level of exposure (1.752 mg/l with four hours of exposure). This study is adequate to establish a Category IV toxicity with regard to inhalation exposure for Technical Metolachlor.

In a test involving a 6 pound per gallon E.C. formulation, the acute inhalation LC-50 was found to be greater than 257 mg/l of air (with four hours of exposure) in the albino rat (Affiliated Medical Research, Incorporated 1974c). However, in the test for acute inhalation LC-50 for an 8 pounds per gallon E.C. formulation, the gross pathology raw data indicate that the test material had an observable effect at both dosage levels in producing areas of consolidation on the lobes of the lungs. But the failure of this study to provide data on particle size distribution invalidates the study, and it cannot be used to determine the acute inhalation toxicity category for the 8 pounds per gallon E.C. The available data, then, places the existing E.C. formulation of 6 lbs. per gallon or less in Category IV with regard to acute inhalation toxicity. The inhalation LC-50 for the 8 pounds per gallon is a data gap.

Acute Delayed Neurotoxicity

This type of data is needed only if the active ingredient or any of its metabolites, degradation products, or impurities cause esterase depression or are structurally related to a substance that induces the specific neuropathy, delayed neurotoxicity. Metolachlor is a chloroacetanilide herbicide and is not expected to cause esterase depression or delayed neurotoxicity. Therefore, this test is not required for Technical Metolachlor.

Local Irritation

Primary Eye Irritation

The minimum testing needed to evaluate eye irritation potential is one test for each technical and formulation, conducted on the albino rabbit.

A study of eye irritation for the Technical was conducted by Sachsse (1973a) on the New Zealand rabbit. In that study 0.1 ml of Technical Metolachlor was used. The test was evaluated using the system of Draize (1959) and produced the following eye irritation and indices at 24 hours and 7 days:

Cornea:	0
Iris:	0
Conjunctivae:	0

This study establishes that Technical Metolachlor is non-irritating to the rabbit eye (Category IV).

In a test involving a 6-pound per gallon E.C. formulation, the data indicates that this formulation is a severe irritant which can cause irreversible corneal opacity in the unrinsed albino rabbit eye (Affiliated Medical Research, Incorporated, 1974i). In a study involving an 8-pound per gallon E.C. formulation (Scribor and Mastri, 1977a): the results from tests conducted with unrinsed eyes showed moderate corneal opacity (reversed in 7 days) and conjunctival effects (partially reversed in 7 days); the results from tests on rinsed eyes showed slight iris and moderate conjunctival effects (reversed in 3 days). The available data, then, places existing E.C. formulations in Category I (for 6 lbs.) or Category II (for 8 lbs.) with regard to primary eye irritation. Considering the lack of irritation effects due to the active ingredient alone (in the Technical), and the difference in eye irritation effects between the two formulations, the degree of eye irritation produced by Metolachlor formulations appears to be directly dependent upon the type and amount of inert formulants used.

Primary Dermal Irritation

The minimum testing needed to determine the potential for primary dermal irritation is one test conducted on a mammal, preferably the albino rabbit, for each technical and formulation.

Sachsse (1973b) evaluated the dermal irritation of Technical Metolachlor on the New Zealand rabbit. The test was evaluated using the system of Draize (1959) and resulted in a primary irritation index of 0.1. This information is sufficient, and it establishes that Technical Metolachlor is non-irritating to rabbit skin (Category IV).

In a test involving a 6-pound per gallon E.C. formulation, the primary irritation index was determined to be 1.62 (Affiliated Medical Research Incorporated, 1974h). In a test involving an 8-pound per gallon E.C. formulation, the dermal irritation was described as: moderate erythma, edema, and second degree burns at 72 hours (Scribor, 1971). Based on the above data, it is anticipated that E.C. formulations of Metolachlor as high as 8 pounds per gallon can be expected to produce not less than a primary irritation index value of 1.62 (mild irritation) in the albino rabbit. The available data, then, places existing E.C. formulations in Category II (for 8 lbs.) or Category IV (for 6 lbs.) with regard to primary dermal irritation. As with eye irritation, the degree of dermal irritation appears to be dependent upon the type of inert components used in the formulations rather than on the concentration of the active ingredient, Metolachlor.

Subchronic Effects and Neurotoxicity

Subchronic Oral Dosing

Testing should be performed in at least 2 mammalian species. One species should be a generally recognized strain of laboratory rat while the second species should be a non-rodent.

Three-month feeding studies were performed with Sprague-Dawley rats (Coquet, Galland, Guyot, Fouillet, and Rouaud, 1974d) and with beagle dogs (Coquet, Galland, Guyot, Fouillet, and Rouaud, 1974c). The Agency determined that the histopathology evaluations for both the rat and the dog study were not performed by a pathologist. Subsequently, the histopathology from the 90-day dog study was re-read by a qualified pathologist, and this re-evaluation of histopathology was submitted to the Agency, allowing this study to fulfill the Guideline's requirement for non-rodent subchronic oral dosing.

Because a two-year rat chronic feeding study was initiated in support of tolerance petitions (see discussion below under 'Chronic Effects'), the Agency decided to waive the need for a re-evaluation of the histopathology of the other 90-day feeding study - the one on rats (Coquet et al, 1974d). However, because that two-year rat feeding study was subsequently found to be invalid (again see discussion below under 'Chronic Effects'), the Agency presently requests (as an interim requirement until the two-year chronic feeding study on rats is re-done) the additional re-evaluation of the histopathology for the subchronic feeding study on rats by Coquet et al (1974d). This histopathology review for the subchronic feeding study on rats thus presently constitutes a data gap for Metolachlor.

A six-month (180 day) dog study (IRDC, 1979) was performed in support of certain tolerance petitions in lieu of adequate chronic data. Various questions about this study's methodology and statistical calculations have now been answered, and the Agency concludes that the 'no observed effect level' (NOEL) in the study was 100 ppm.

Subchronic 21-Day Dermal

The minimum testing needed is one study in one mammalian species. Although no data is presently available on Technical Metolachlor, a 21-day dermal study was performed using Metolachlor 6E (68.5% active ingredient) and is considered to provide sufficient information (Affiliated Medical Research Inc., 1974f). The study reported no significant evidence of systemic effects at a dose level of 540 mg Metolachlor per kilogram, per day. At 1080 mg Metolachlor per kilogram, per day, the only indication of systemic effects was decreased body weight gain.

Subchronic 90-Day Dermal

This study is not needed because the existing acceptable end-uses should not result in repeated human skin contact for this long a period.

Subchronic Inhalation

The existing acceptable end uses should also not result in repeated inhalation exposure at a concentration which is likely to be toxic as determined by an acute inhalation test. Therefore, this study is not needed.

Subchronic Neurotoxicity

Metolachlor is a chloroacetanilide and is related in structure to registered chemicals that have not induced neuropathy nor delayed neurotoxicity, as evidenced by the results of an acute test. This type of data is therefore not needed.

Sensitization

The minimum data needed to assess dermal sensitization can be provided by an intradermal test on one mammalian species, preferably the male albino guinea pig. The first evaluation of dermal sensitization was conducted by Affiliated Medical Research, Incorporated (1974g). Inappropriate methodology (the patch test) and the lack of sensitization in a positive control invalidate this study and preclude its use in the regulatory process. A second study (Sachsse, 1977) used the intradermal injection method: Technical Metolachlor dissolved in the vehicle (propylene glycol) and the vehicle alone (negative control) were intradermally injected into the skin of Pilbright guinea pigs. Positive reaction was demonstrated in animals injected with Technical Metolachlor dissolved in the vehicle; there was no reaction in animals injected with the vehicle alone. Based on this second study, which is sufficient, it is established that Technical Metolachlor is a skin sensitizer in guinea pigs. Though there are no studies available in which the E.C. formulations were directly tested, it is anticipated that E.C. formulations of 6 or 8 lbs. ai/gal will also cause skin sensitization in guinea pigs.

Chronic Effects

Chronic testing should be available on at least one mammalian species. The species should normally be a generally recognized strain of the laboratory rat, and the route of administration should be through the animals' diet.

One two-year feeding study on the rat was performed (Kennedy, 1976b), but the Agency found the study to be invalid because of several deficiencies in protocol, including the fact that dose levels were not verified by an analysis of the diet. The study does offer supplementary information on Metolachlor's potential oncogenicity (see below). Because this study thus cannot be used to fulfill the guidelines requirement, the rat chronic feeding study for Metolachlor is currently a data gap.

Oncogenicity

For the adequate assessment of oncogenicity, studies are needed in two mammalian species: normally, the mouse and the laboratory rat.

A mouse study was conducted with Charles River CD-1 albino mice (50 of each sex) at levels of 0, 30, 1,000, and 3,000 ppm fed in the diet. The duration of the study was 18 months for males and 20 months for females. It was conducted by Industrial Bio-Test Laboratories (IBT) and validated by Ciba-Geigy Corporation (Gesme, Albanese, Marias, and Arceo, 1977). Because EPA suspected that some of the toxicology studies performed by IBT were deficient to the point of not being valid for the support of pesticide registrations, Ciba-Geigy initiated a new mouse oncogenicity study. However, the Agency's subsequent in-depth evaluation of the IBT study found that, despite certain deficiencies in good laboratory practices and animal husbandry techniques, the raw data supported the reported negative results. The IBT study therefore satisfies the requirement for mouse oncogenicity testing, and the Agency concludes from it that Metolachlor is not oncogenic to mice at the given dietary dosages. Although the additional mouse data is not required, the second mouse oncogenicity study is still underway and the Agency will evaluate the results if and when they are submitted.

Though the two-year chronic feeding study on rats discussed in the 'Chronic Effects' section above) (Kennedy, 1976b) was not valid for the fulfillment of the chronic feeding data requirement, it did offer supplementary information for oncogenicity by reporting no evidence that Metolachlor is oncogenic. Nevertheless, this study does not fulfill the guideline requirement for an oncogenicity test in the rat, and this constitutes a data gap. An oncogenic evaluation performed on the animals in the required two-year rat chronic feeding study would suffice for this requirement on oncogenicity in the rat.

Mutagenicity

The following studies represent only the minimum requirements for data on the potential heritable effects of a pesticide: (1) a mammalian *in vitro* point mutation test; (2) a sensitive sub-mammalian point mutation test (bacteria, fungi, insect); (3) a primary DNA damage test (i.e., sister chromatid exchange or unscheduled DNA synthesis; and (4) a mammalian *in vitro* cytogenetics test. If the last test suggests a positive result, a dominant lethal or heritable translocation test may be required.

After results from these test systems and other toxicology disciplines have been considered, additional testing may be required to further characterize or quantify the potential genetic risks. Although the Agency's mutagenic testing requirements are not final, the standards for these tests should be based on the principles set forth in the Proposed Guidelines (FR 43, No. 163, August 22, 1978). Protocols and choices of test systems should be accompanied by a scientific rationale. Substitution of test systems for those listed above will be considered after discussion with the Agency.

These requirements should be considered an interim guide and not final Agency policy. However, the Agency has considered the above testing scheme to be a reasonable minimum requirement.

In accordance with the fact that the above policy on mutagenicity testing is an interim one, the minimum testing presently being required to assess mutagenicity for Metolachlor is testing in only two experimental systems. The potential of Metolachlor to cause genetic changes has been tested for in a bacterial system utilizing activation by mammalian microsomes (Arni and Muller, 1976), and in an *in vivo* system to test the effect on developing sperm in the mouse (Ciba-Geigy Limited, 1976a).

The bacterial (*Salmonella*) system was tested for base substitutions and point mutations at various ranges (10, 100, 1,000 and 10,000 ug/plate). No increase in background mutation rates was observed. Nor were there any effects noted, in the mouse study, on fertility rates, or on zygote or embryo survivals, after single oral doses of 100 and 300 mg/kg. Also, no malformations of resulting embryos were reported. From these two studies, which are presently sufficient for mutagenicity testing, no evidence arose to suggest that Metolachlor has any mutagenic potential. Further mutagenicity testing on Metolachlor may later be required when a final policy on mutagenicity testing has been established.

Teratology

The minimum data needed to evaluate the potential fetotoxic or teratogenic effects of a pesticide are tests in two mammalian species. A study of the teratogenic effects of Technical Metolachlor on rats was conducted by Fritz (1976). The study found that doses of either 0, 60, 180, or 360 mg/kg/day during 6 to 15 days of gestation did not effect the offspring of female Sprague-Dawley rats. No fetotoxic effects of the compound were observed. The only possible effect on the rats was a decrease in food consumption at the highest dose during the first 1/3 of the experiment which may indicate that this was the beginning of toxic maternal doses. This study is sufficient for the assessment of teratology in one species of mammal, and does not show any evidence of a teratogenic hazard for Metolachlor. Data is still needed on a second mammalian species.

Reproductive Effects

The minimum data needed for measuring reproductive effects can be provided by one rat study lasting two generations. The one available study (Smith and Adler, 1978) had significant deficiencies including problems in animal husbandry, mating performance and success (possibly caused by poor animal health), and observation records, which cause the Agency to consider its conclusions as only 'supplementary' information. The study suggests no reproductive effects, but Metolachlor still requires a satisfactory multigeneration reproduction study.

DISCIPLINARY REVIEW

Toxicology Profile
Toxicology Hazard Assessment
Generic Data Gaps
Product Specific Data Gaps
Suggested Labeling

Toxicology Profile

Technical Metolachlor: Sufficient data were available to support an assessment of the Technical's acute toxicity. The relatively high acute oral LD-50 in rats (2780 mg/kg) and the emetic effects in dogs indicate a low acute oral toxicity to humans. Dermally, at least in the rabbit, Metolachlor does not appreciably penetrate intact skin. Doses of up to 10,000 mg/kg caused no signs of toxicity and little irritation. Pending receipt of data on abraded skin, it would appear that Metolachlor would not be readily absorbed through human skin. The lack of toxic signs or irritation from high acute dermal exposure in test animals indicates that Technical Metolachlor has a low dermal toxicity to humans. Testing of acute inhalation toxicity in rats failed to elicit any deaths at the maximum achievable concentration (1.752 mg/l for 4 hours exposure), and so a low inhalation toxicity to humans for manufacturing-use Metolachlor may be expected.

Information was also available on the irritation and sensitization potential of Technical Metolachlor. In a primary eye irritation study conducted on albino rabbits, no signs of irritation were observed. Based on the rabbit as an indicator species, Metolachlor is not expected to be irritating to human eyes. A dermal sensitization study in guinea pigs indicated that Metolachlor was a skin sensitizer to that species. Metolachlor should therefore be considered a potential skin sensitizer in humans.

A six-month dog study indicated an oral 'no observed effect level' (NOEL) of 100 ppm, and this is presently the only NOEL value available for tolerance setting. (See Residue Chemistry 'Tolerance Reassessment'.) The one available chronic (two year) feeding study was not valid, though it offered evidence to support the conclusion of the one oncogenicity study in mice that Metolachlor is not oncogenic by the dietary levels tested. Though data on a second species will be needed, there was one study of teratogenic effects in rats, and it reported no teratogenic or fetotoxic effects due to Metolachlor at the doses tested. Metolachlor has been tested in two systems for mutagenicity: a bacterial system, and an *in vivo* system in the mouse. No evidence is presented in either study to suggest that Metolachlor has any mutagenic potential.

The currently registered Metolachlor Technical product falls into the following 'Toxicity Categories' [see 40 CFR 162.10 (h)(1)]:

Acute Oral Toxicity: Category III
Acute Dermal Toxicity: Category III
Acute Inhalation Toxicity: Category IV
Primary Eye Irritation: Category IV
Primary Dermal Irritation: Category IV

Emulsifiable Concentrate: For the E.C. formulations of 6 and 8 lbs, ai/gallon, the reported values of 1,890 mg/kg or higher indicate a relatively high acute oral LD-50 in rats, implying a low acute oral toxicity for humans. Dermally, at least in the rabbit, the two existing E.C. formulations of Metolachlor do not appreciably penetrate intact skin, and doses of up to 3,038 mg/kg produced no signs of toxicity in the New Zealand rabbit. From existing data, it can thus be assumed that the E.C. formulations of 6 and 8 lbs. ai/gallon present a low overall acute toxicity to humans via the intact dermal route. The test on acute inhalation was only available for the six pound per gallon E.C., and demonstrated a very low acute inhalation toxicity. A test for the eight pounds per gallon E.C. is required because of the difference in volatile inerts.

The potential for local irritation and sensitization appears to be significant. Based on the albino rabbit as an indicator species, the 8 lbs. ai/gallon formulation will produce moderate erythma, edema, and second degree burns (severe irritation). A dermal sensitization study in guinea pigs indicated that two registered E.C. formulations are also potential skin sensitizers in humans. In a primary eye irritation study conducted on the albino rabbit, the 6 lbs. ai/gallon formulation of Metolachlor was found to cause irreversible corneal opacity and severe irritation in unrinsed eyes, which indicates a potential for serious human eye irritation due to that formulation.

The currently registered Metolachlor Emulsifiable Concentrate Products fall into the following 'Toxicity Categories' [see 40 CFR 162.10 (h)(1)]:

Emulsifiable Concentrate (6 lbs. active ingredient per gallon):

Acute Oral Toxicity: Category III
Acute Dermal Toxicity: Category III
Acute Inhalation Toxicity: Category IV
Primary Eye Irritation: Category I
Primary Dermal Irritation: Category IV

Emulsifiable Concentrate (8 lbs. active ingredient per gallon):

Acute Oral Toxicity: Category III
Acute Dermal Toxicity: Category III
Acute Inhalation Toxicity: undetermined
Primary Eye Irritation: Category II
Primary Dermal Irritation: Category II

Toxicology Hazard Assessment

Technical Metolachlor: Considering first the potential for human (or domestic animal) exposure to manufacturing-use Metolachlor, it was stated in the Exposure Profile that there is little likelihood of oral exposure, and that because of the low vapor pressure of the necessarily viscous liquid, there is also little chance of inhalation exposure. The most likely type of exposure for persons involved in the handling, storage, shipment, or re-formulation of Technical Metolachlor is a repeated dermal exposure.

Because of Technical Metolachlor's low acute oral toxicity, and very low inhalation toxicity, we may dismiss these unlikely exposure routes as significant sources of hazard. The occasional occular exposure is also not of serious concern, as no eye irritation effects would be expected. But with respect to dermal exposures, although it has been shown that Metolachlor is not readily absorbed by the skin, the likelihood of repeated dermal exposures raises two concerns: first, Metolachlor has been observed to elicit a dermal sensitization reaction; second, although no positive evidence of general chronic, teratogenic, fetotoxic, oncogenic, or mutagenic effects has so far been presented, the available information is presently insufficient to satisfy all the Agency's requirements for the study of chronic effects. Thus the risks to humans caused by repeated dermal exposures to a Technical Metolachlor solution cannot be concluded at this time, and the only presently known hazard of manufacturing-use Metolachlor is the potential for dermal sensitization for factory, transport, or re-formulation workers.

Emulsifiable Concentrate: The hazards to humans and domestic animals that may arise from the end-use of an agricultural pesticide are of three kinds: those hazards to humans which arise in the tank mixing, dilution, application, storage, or disposal of the end-use chemical; those hazards to humans and domestic animals which arise as a result of ambient residues from pesticide application, storage, or disposal, including residues in air, water, and edible wildlife; and, finally, those hazards to humans or domestic animals which may arise as a result of anticipated residues in harvested food or feed. The first two kinds are considered here in the Toxicology chapter. The last kind will be considered in the Residue Chemistry chapter.

As was stated in the Exposure Profile, there is little chance for accidental oral exposure to a soil-sprayed pesticide that is not mixed with foodstuffs before application. But there is a chance for dermal and eye exposure for chemical applicators who are tank mixing, diluting, or loading. There is also a chance of inhalation exposure for applicators, agricultural workers, and livestock in the proximity of the spraying. Though spray drift properties of Metolachlor applications have not been established, and Metolachlor may therefore not be applied aerially, ambient air residue exposures may conceivably occur to persons or livestock outside the ground-spray area. Due to leaching and a stability to hydrolysis, residues may also be found in nearby freshwater streams or ponds, thus posing the threat of repeated exposures to livestock drinking the water or grazing on nearby plants, or to persons ingesting contaminated fish or water.

The routine outdoor agricultural field use of Metolachlor could directly result in a number of minor hazards for humans. The data show that it is possible for a Metolachlor formulation to cause irreversible corneal opacity and severe iritation to an applicator whose eyes are unprotected during mixing, loading, or diluting. Similarly, an applicator with unprotected hands or face could run an acute risk of erythma, edema, and second degree burns due to contact with certain formulations. If dermal exposures to any Metolachlor formulation are repeated, there is a risk of a sensitization reaction. Finally, though the active ingredient is not readily absorbed through the skin, various chronic or reproductive effects from a repeated dermal or inhalation exposure to a Metolachlor formulation cannot presently be ruled out.

Ambient residues from the ground-spray application of a Metolachlor formulation may present parallel, though significantly lesser, hazards to persons or livestock outside the spray area. Of potential concern are the long-term, repeated exposures for livestock or humans drinking contaminated water or feeding on nearby aquatic and plant life, possibly resulting in undetermined chronic effects.

Generic Data Gaps

The following are gaps in the Toxicology data base which will be used to support registrations under this Metolachlor Standard. After each gap is listed the section in the Proposed Guidelines of August 22, 1978 (FR Part 163) which describes that type of study and when it is required.

1)	Subchronic Oral Dosing - Acceptable pathology evaluation is required for the rat study.	163.82-1
2)	Chronic Feeding - A chronic feeding study using the laboratory rat is required.	163.83-1
3)	Oncogenicity - An oncogenic evaluation performed for the chronic feeding study [see (2) above], or an oncogenicity study in a mammalian species other than the mouse (preferably the laboratory rat). The Agency is also awaiting the results of the second mouse study.	163.83-2
4)	Teratology - A teratology study in a mammalian species other than the rat is required.	163.83-3
5)	Reproduction - A multi-generation reproduction study on one mammalian species (preferably the laboratory rat).	163.83-4

Product Specific Data Gaps

The following is a "product specific" data gap for Toxicology which needs to be filled in order to maintain in effect a current registrations under this Standard. After the gap is the section in the Proposed Guidelines (August 22, 1978, FR Part 163) which describes that type of data and when it is required.

For Emulsifiable Concentrate Metolachlor (8 lbs. ai/gallon):

1)	Acute inhalation toxicity study.	163.81-3

Suggested Labeling

See the Metolachlor Standard's 'Regulatory Rationale' for a discussion of the levels of acute toxicity which the Agency will consider acceptable, and the second chapter of the Standard for a listing of the specific label statements appropriate to the acceptable 'Toxicity Categories.' Section 162.10 of the CFR 40 explains the Agency's established toxicity labeling requirements as they relate to the 'Toxicity Categories'.

The only toxicology labeling suggested by the available data that does not follow directly from Metolachlor's 'Toxicity Categories' is a precaution concerning dermal sensitization: "May cause skin sensitization. Wear gloves and protective clothing while handling or using this product. Wash thoroughly after handling. Remove and wash contaminated clothing before re-use."

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RESIDUE CHEMISTRY

TOPICAL DISCUSSIONS

Metabolism in Plants
Metabolism in Animals
Analytical Methodology
Residue Data
Present Tolerances

Metabolism in Plants

The absorption, distribution, and metabolic fate of Metolachlor were investigated in corn plants grown under field and greenhouse conditions (Sumner and Cassidy, 1974c,d) and in soybeans grown under greenhouse conditions only (Sumner and Cassidy, 1975).

Ring-labeled Metolachlor was applied as a pre-emergence treatment at 2 lbs. ai/acre. For corn, it was dissolved in nutrient solution at a concentration of approxiamately 2 ppm and applied to field and greenhouse soils. For soybeans, it was added to soil and plantings were incubated in the greenhouse. The maximum levels of residues found in the various plant parts, based on total radioactivity, were as follows: corn grain, greenhouse and field, 0.05 ppm and 0.02 ppm, respectively; corn forage, greenhouse and field, 0.72 and 0.17 ppm, respectively; soybeans 0.17 ppm, soybean hay 2.66 ppm, soybean oil 0.01 ppm and soybean meal 0.14 ppm. These data show that the total residues in soybeans are higher than those in corn.

The metabolism of Metolachlor by corn plants consists of a major and a minor pathway. The figure in the 'Disciplinary Review' at the end of this chapter depicts these pathways for both corn and soybean plants (Marco 1975).

When corn plants were grown in soil treated with Ø-^{14}C-Metolachlor at 2 lbs. ai/acre (Sumner and Cassidy 1974d), extracts of 4-week old corn plants contained less than 10% of the extractable radioactivity present in the organic fraction. Very little, if any, of the activity was present as parent Metolachlor. More than 80% of the remaining activity was found in the polar fraction. TLC characterization indicated the presence of at least 10 metabolites. The highly polar nature of these metabolites indicated conjugation of the parent and/or its metabolites had occurred with natural products such as amino acids, sugars, or sugar acids (Sumner and Cassidy, 1974c).

One metabolic pathway in the corn plants involves conjugation of Metolachlor with glutathione (Sumner and Cassidy, 1974b). Fourteen percent of the radioactive Metolachlor recovered from corn leaves was found conjugated with glutathione. It appears that degradation occurs through a thio-ether bond forming a glutathione conjugate via the reactive chloroacetyl moiety of Metolachlor.

Metabolites, which upon hydrolysis, produce 2-[(2-ethyl-6-methylphenyl) amino]-1-propanol (HP-001) and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone (HP-002) were found to be common in plants and in animals, from high level feedings of Metolachlor (Hambock, 1974a,b,c; Mattson, 1975). When partly purified plant conjugates were cleaved by a reduction reaction with

Raney nickel, which breaks thio-ether bonds (Gross, 1974a and Gross, 1974b), two compounds, N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide (MET-005), and N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methylethyl)acetamide (MET-006) were produced, indicating that these compounds were moieties of sulfur-bonded conjugates. These two compounds represent 80% of the radioactivity extracted from the corn leaves. They were positively identified by GLC and mass spectrometry.

Further residue characterization, involving rigorous HCl hydrolysis (Sumner, Thomas, and Cassidy, 1975), showed the presence of either 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol (HP-001) or 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone (HP-002). These data suggest that the compounds present before hydrolysis are predominantly alpha-thioglycoside metabolites and the alpha-oxygen glycoside analogues. The relative amounts of the compounds indicate that the major pathway of metabolism involves conjugation with glutathione, breakage of the thio- bond to form the mercaptan, conjugation of mercaptan with glucuronic acid, hydrolysis of methyl ether, and conjugation of the alcohol with a neutral sugar. A minor pathway assumes chloro replacement by hydroxyl. The same pathway may also involve direct conjugation with glucuronic acid, followed by demethylation and conjugation of the hydroxyl with a neutral sugar, all forming oxo- conjugates.

When radiolabeled Ø-^{14}C-Metolachlor was applied to growing soybeans (Sumner and Cassidy, 1975b), characterization of the extracted residues indicated that the metabolic pathways in soybeans are similar to those observed in corn. Thin-layer chromatography and partitioning data indicated that higher concentrations of less polar metabolites will occur in soybeans when compared to corn grain.

Because it has been suggested that the chloroacetyl group could split off as monochloroacetic acid and occur as part of the terminal residue, Toxicology reviewers expressed concern about the possible presence of monochloroacetic acid as a component of the residues of Metolachlor, resulting from metabolism or degradation of the parent compound. However, Residue Chemistry reviewers can find no reason to expect monochloroacetic acid to occur as a residue following the use of Metolachlor. While there is no definitive data on the matter, the Agency has postulated, based upon the unique chemical and biological stability of the amide bond and the relatively unstable carbon-chlorine bond in Metolachlor, that any hydrolysis of the amide would be preceded by displacement of the chlorine. Consequently, the presence of monochloroacetic acid as a product of metabolism is not likely to occur.

The above studies adequately define the fate of Metolachlor in soybeans and corn for the purposes of establishing tolerances.

Though no studies were available for peanuts or sorghum, the metabolism studies for corn and soybeans are adequate to reflect the nature of Metolachlor residues in peanuts and sorghum. In other words, the Agency is taking the position that the nature of the residues in peanuts and sorghum is similar to that of corn and soybeans. No metabolism studies are yet available for root crops such as potatoes. Because the residue in root crops may differ from that of non-root crops, we are unable to apply the data on corn and soybeans to root crops such as potatoes. If a tolerance is to be established root crops, root crop metabolism data will be needed.

Metabolism in Animals

Metolachlor is rapidly metabolized and almost totally eliminated in the urine and feces of ruminants (goats), non-ruminants (rats), and poultry (Roger and Cassidy, 1974a; Hambock, 1974a; Guth, 1974). These findings were made in studies using both unlabeled and ^{14}C-ring-labeled Metolachlor. Metolachlor per se was not detected in any of the excreta or tissues.

Additional studies with goats (Counselman and Roger, 1973; Roger and Cassidy, 1974a,b) confirmed the finding that the urine and feces contain almost all the metabolized products.

In animals, trace amounts of metabolized Metolachlor were found in kidneys, liver, blood, and milk (Biometric Testing Incorporated, 1973; Hambock, 1974a, b,c; Schenker, 1975a).

No residues were found in eggs, meat, or fat samples of laying chickens. The only metabolite found, in the liver (at 0.02 - 0.03 ppm), was the one which upon hydrolysis yields HP-001 (Mattson, 1974, 1975). No precursor of the hydrolysis product HP-002 was found in the liver (Guth, 1974).

When ^{14}C-labeled metabolites of Metolachlor, bio-synthesized in corn, were fed to goats, no parent Metolachlor nor any metabolites were found in the animals' tissues or milk (Ciba-Geigy Limited, 1973; Schenker, 1974, 1975b).

It is concluded that the metabolism of Metolachlor in animals appears to be similar to and as complex as that in plants. Whereas plants retain their metabolic products, animals eliminate their Metolachlor metabolic products almost entirely. Various studies with unlabeled Metolachlor and ^{14}C-ring labeled Metolachlor fed to different animals indicate clearly the identity and the amounts of the metabolites which result as residues in the excreta, tissues, milk, and eggs.

Although the exact metabolic pathway of Metolachlor in animals is not known, the available metabolic studies adequately delineate the fate of Metolachlor in animals for the purposes of establishing tolerances for corn grain and soybeans. (For an evaluation of rat metabolism data, please see Toxicology Chapter.)

Analytical Methodology

Metolachlor in Corn and Soybeans

The residue data submitted for corn were obtained by the use of methods AG-265 (Balasubramanian, Gold, and Ross, 1974) and AG-277 (Balasubramanian, Aziz, and Ross, 1975). The residue data for soybeans were obtained by Method AG-286 (Aziz and Ross, 1975). Most of the corn residue data were obtained by Method AG-265. This method utilizes HCl to hydrolyze Metolachlor and those metabolites which are capable of conversion to 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol (HP-001).

In Method AG-265, fifty grams of ground or chopped sample is refluxed with 250 ml of 6N HCl for 16 hours. The aqueous extract is filtered off, neutralized, and made basic with NaOH solution and extracted twice with hexane. The combined hexane extracts are chromatographed on an alumina column. The residues of HP-001 are eluted using 5% ether in hexane. The eluate is evaporated and the residues are taken up in 0.5 ml of benzene. An aliquot of the sample solution is injected into a gas chromatograph equipped with a Coulson eletrolytic conductivity detector. Known amounts of HP-001 are used for standardization. Peak heights are compared with those of the standard for quantification. Residues are expressed as parent Metolachlor equivalents using the 1.47 factor.

The method was validated by the petitioner in three ways: (1) fortification with the determined compound, HP-001; (2) fortification with parent Metolachlor, (CGA-001); and (3) comparison of GLC analyses of ^{14}C-labeled residues from metabolism study samples with total ^{14}C-combustion analyses of duplicate samples.

Recovery for samples of grain, forage, silage, and stover fortified at levels of 0.05-2.0 ppm with HP-001 averaged 81%. All control samples were determined to have <0.03 ppm (the method sensitivity). Fortification studies using parent Metolachlor averaged 63% for levels of 0.05-0.2 ppm in stover.

The total ^{14}C-activities in samples of corn plants taken from both the field and greenhouse studies were determined by combustion (Hermes, 1972). The combustion technique determined all residues (both extractible and nonextractible) after conversion to $^{14}CO_2$. The residues (expressed as CGA-001) determined by Chemical Method AG-265 ranged from 12% (mature crop) to 27% (immature forage or silage) of the total residues found by combustion techniques. Comparisons were also made of the total extractible residues by the chemical method vs. the ^{14}C-combustion method using two extraction solvent systems, HCl, and combined chloroform-methanol solvent. About 50-60% of the ^{14}C-residues in mature corn were extractable using either method. The chemical method determined 20-30% of the total extractable ^{14}C-residues.

Except as stated directly below, method AG-265 (Balasubramanian, Gold, and Ross, 1974) was found to be specific in the presence of other pesticides with established tolerances on corn. Six pesticides were not available for testing: EPN, Vegadex, Avadex, Landrin, 4-amino pyridine, and 2-(thiocyanomethylthio)-benzotriazole. An alternate column liquid phase is available and provides additional specificity for residues of Metolachlor.

Method AG-277 (Balasubramanian, Aziz, and Ross, 1975) is a modification of AG-265 which includes partitioning, clean-up, derivatization, and micro-coulometric GLC steps determining two hydrolysis products: 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol (HP-001) and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone (HP-002).

Residues of Metolachlor (CGA-001) in corn grain, ears, forage, fodder and stover are converted to a mixture of HP-001 and HP-002 by refluxing 16 hours with 6N HCl. The filtered acid extract is partitioned with dichloromethane to extract the HP-002 into the organic phase. The aqueous phase containing HP-001 is made strongly basic with 50% sodium hydroxide and subjected to distillation-partition into isooctane using a Bleidner apparatus. The isooctane phase containing HP-001 is cleaned up by using an alumina column. HP-001 is determined with a gas chromatograph equipped with a Coulson electrolytic conductivity nitrogen detector. It is quantified by comparing it with the peak height of a standard amount of HP-001 and then calculated as CGA-001 using the 1.47 equivalence factor.

The dichloromethane phase containing HP-002 is washed with 5% sodium carbonate solution and further cleaned up using an alumina column. The chloroethanol derivative of HP-002 is formed by reaction with boron trichloride/2-chloroethanol at 90°C for 15 minutes. The derivative is partitioned into hexane and an aliquot is cleaned up using silica gel and alumina columns. A gas chromatograph equipped with Dohrmann microcoulometric chloride detector is used for analysis. For quantification, the peak area is compared to that of peak areas of derivatized standard HP-002. Residues are calculated as COM-001 using the conversion factor 1.13.

Controls for HP-001 usually ranged from less than 0.02 ppm to 0.05 ppm. In some samples, the controls ranged up to 0.1 ppm due to an interfering peak. We consider the sensitivity of the method for HP-001 to be 0.05 ppm or less. Recoveries for 69 samples of fodder, forage, grain, or ears, fortified at 0.02 and 0.20 ppm, ranged from 57-115% with an average of 65%. Typical recovery data residues of HP-002 for samples fortified at 0.05-0.20 ppm ranged from 45-102% with an average of 62%. The method sensitivity is considered to be 0.10 ppm for HP-002 when calculated as COM-001.

The method used for the soybean residue data is Method AG-286 (Aziz and Ross, 1975). This method, "Analytical Method for the Determination of Residues of Metolachlor Soybean Metabolites (as HP-001 and HP-002) by Acid Hydrolysis," is the method for regulatory enforcement which will be incorporated in the FDA pesticide Analytical Methods, Vol. II. Method AG-286 was tried out in one of EPA's laboratories and found to be acceptable.

Method AG-286 was tested for specificity with 54 of the 58 pesticides registered on soybeans. DC-200 and Carbowax 20 M are available as alternate liquid phases to enhance the specificity of the GLC determinative steps.

The analytical methods are also adequate for the enforcement of tolerances on peanuts and sorghum. However, the absence of data indicating the significant components of residues in root crops precludes valid conclusions on the adequacy of these methods for the determination of Metolachlor residues in root crops for enforcement purposes.

Metolachlor in Animal Tissues

Analyses of meat, milk, and egg samples were conducted by methods reported in Basle REM 5/74 (Hormann, Guth, Formica, and Schenker, 1974) and Basle REM 2/75 (Ramsteiner and Karlhuber, 1975). Analytical method (REM 2/75) accounts for "combined residues" of Metolachlor, determined as HP-001 and HP-002.

In the first method (REM 5/74), the herbicide and the potential metabolites and/or conjugates in animal products are subjected to acidic hydrolysis. The resulting solution is made alkaline before steam-distillation; extraction of residues into isooctane is effected by means of a steam distillation-extraction head. The HP-001 fraction is cleaned up by using an alumina column and, if necessary, by TLC.

The HP-001 "residues" are detected by gas chromatography/mass spectrometry. This method is a minor modification of AG-265 and was used for the gas chromatographic analysis of milk, blood, meat, fat, liver, kidney, egg white and egg yolk. The limits of detection for HP-001 are 0.006 ppm for milk, 0.015 ppm for eggs and chicken tissues, and 0.02 ppm for cow tissues.

The second method (REM 2/75) determines all residues which are hydrolyzed by acid to HP-001 and HP-002. HP-002 is converted to a derivative which is determined by gas chromatography. This method for animal tissues involves minor modifications of Method AG-286. The reported limits of detectibility are 0.01 ppm in milk, and 0.04 in for meat, liver, and kidney.

Method REM 2/75, CGM-001, "Determination of Total Residues in Material of Animal Origin" (Ramsteiner and Karlhuber, 1975), was tried on beef liver in one of EPA's laboratories. Samples fortified in duplicate with HP-001 gave 99% and 100% recovery. Samples fortified in duplicate with HP-002 showed 43% and 45% recovery.

Methods AG-286 and REM 2/75 were found to have adequate specificity and are judged satisfactory for enforcement purposes.

Residue Data

Field residue data for Metolachlor should reflect the use with respect to dosage, mode of application, number and timing of treatments, formulations used and geographical areas represented. Pre-plant soil treatments for grain crops should include examination of foliar parts of the plant during the growing season as well as analyses of the harvested grain.

The analytical methods used to generate the residue data involve a conversion of residues of Metolachlor and its metabolites (through hydrolysis) to 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol (HP-001) and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone (HP-002). The resulting residues from the application of Metolachlor are accordingly expressed as HP-001 and HP-002, or combined as total residue and calculated as Metolachlor.

A storage stability study of Metolachlor residues in corn fodder and grain was performed to ensure that results obtained for samples stored prior to analysis are valid (Gold and Kahrs, 1975b). Samples of corn fodder and corn grain were fortified with Metolachlor at 1.0 ppm and 0.2 ppm, respectively. The samples were kept frozen at -15°C and analyzed at pre-determined intervals up to 13 months after storage. The recoveries for the corn fodder ranged from 92-115% of the fortified amount and the corn grain samples ranged from 92-119%.

Several samples of field-treated corn fodder were also monitored during the 13-month storage period. Residues in one sample varied from 0.43-0.39 ppm and residues in another sample ranged from 0.29-0.26 ppm over the 13-month period.

Residues in Corn

The majority of the residue studies on field and sweet corn were performed by the use of a formulation of Metolachlor called 250 EC. No data were submitted regarding the composition of 250 E.C. formulation. The residues of CGM-001 in these studies are determined as HP-001 alone. The HP-002 breakdown product was not determined. These studies were performed in 9 states (Nebraska, Mississippi, Illinois, New York, Texas, Ohio, California, Wisconsin, Indiana). (Tweedy, 1974; Tweedy and Mattson, 1974; Mattson and Kahrs, 1975b.) (Only studies performed with Metolachlor alone are considered here.)

Nine studies with field corn, at 2 lbs. and 4 lbs. ai/acre of 250 E.C., reported residues less than 0.03 ppm of Metolachlor (as HP-001) in grain at intervals of 111-162 days between pre-emergent application and harvest. Three studies with sweet corn at 2 lbs. and 4 lbs. ai/acre of 250 E.C. reported residues of Metolachlor (as HP-001) in ears as less than 0.03 ppm at 61, 67, and 138 days after the pre-emergent application. Two additional studies with field corn and one with sweet corn using the 6E formulation (at 3 and 6 lbs. ai/acre) indicated no detectable combined residues of HP-001 (as Metolachlor) (less than 0.03 ppm) and HP-002 (less than 0.10 ppm) in the grain and fresh ears respectively 62, 92 and 129 days after the application. At a later date two additional studies at 2 lbs. and 4 lbs.ai/acre of 250 E.C. formulation on sweet corn were performed. No detectable residues of Metolachlor as HP-001 (less than 0.03 ppm) or HP-002 (less than 0.10 ppm) were found in the fresh ear sample at 60 and 67 days after the application.

Seventeen residue studies where Metolachlor was measured as HP-001 show forage residues were less than 0.03 ppm at intervals of 34 and 72 days following 1.5 lbs. ai/acre. Residues resulting from 2 lbs. and 3 lbs. ai/acre applications (at 26 to 72 days) range from less than 0.03 to 0.14 ppm, and less than 0.03 to 0.10 ppm, respectively. At intervals of 26 to 64 days, 4 lbs. ai/acre resulted in residues of less than 0.03 to 0.43 ppm; 6 lbs. ai/acre rates showed HP-001 residues at 0.03 to 0.19 ppm.

Silage stage forage residues of Metolachlor (measured as HP-001) resulting from 2 lbs. and 4 lbs. ai/acre range from less than 0.03 ppm to 0.16 ppm, and less than 0.03 ppm to 0.43 ppm, respectively, at intervals from 71 to 112 days after application.

Mature fodder and stover residues ranged from less than 0.03 ppm to 0.44 ppm (measured as HP-001) for both the 2 lbs. and 4 lbs. ai/acre rates.

Eleven studies in which Metolachlor was later measured as combined residues of HP-001 and HP-002 show residues in early forage of less than 0.03 ppm to 0.24 ppm and less than 0.03 ppm to 0.08 ppm for 2 lbs. and 3 lbs. ai/acre treatments, respectively; 4 lbs. and 6 lbs. ai/acre applications resulted in forage residues ranging from 0.04 ppm to 0.64 ppm and 0.03 to 0.19 ppm, respectively.

Silage stage forage showed combined HP-001 and HP-002 residues (as Metolachlor) of 0.08 to 0.14 ppm, 0.04 ppm to 0.12 ppm, and 0.05 ppm to 0.28 ppm for treatments at 1.5 lbs., 2.0 lbs., and 3.0 lbs., respectively. Combined residues from 4 lbs. and 6 lbs. ai/acre treatments were 0.14 to 0.63 ppm and 0.13 to 0.34 ppm, respectively.

Fodder and stover residues for 1.5 lbs., 2.0 lbs., and 3.0 lbs., ai/acre treatments were less than 0.03 to 0.06 ppm, less than 0.03 to 0.23 ppm, and 0.07 to 0.30 ppm.

Combined residues of HP-001 and HP-002 (as Metolachlor) in mature fodder and stover reported in six studies at 4 lbs. ai/acre ranged from 0.07 ppm to 0.90 ppm. Three studies at 6 lbs. ai/acre reported combined residues in fodder ranging from 0.14 to 0.53 ppm.

Because no detectable residues were found in corn grain, no residue data are needed for corn grain by-products (corn oil, corn meal, etc.).

Residues in or on Soybeans

Twenty-three residue studies were performed in eight states representing the major soybean growing areas. (Again, only studies performed with Metolachlor alone are considered here.) Application rates were from 2 to 6 lbs. ai/acre (Mattson and Rolla, 1975; Texas A & M Cottonseed Products Research Laboratory, 1966; Houseworth and Rolla, 1976).

Analyses involved the determination of both HP-001 and HP-002. No detectable residues (less than 0.05 ppm) of HP-002 were found in any of the soybean samples. Residues of HP-001 in the soybeans which ranged from less than 0.03 to 0.09 ppm resulted from application rates of up to 5 lbs. ai/acre; the maximum reported residue was from a 3 lb. ai/acre application. At 6 lbs. ai/acre, residues of HP-001 ranged from less than

0.03 to 0.21 ppm.

Three fractionation studies showed no detectable residues of HP-001 (less than 0.03 ppm) or HP-002 (less than 0.05 ppm) in any fraction (meal, crude and refined oil, soapstock) from soybeans treated at rates of 2 to 5 lbs. ai/acre. At 6 lbs. ai/acre, the only finite residue was found in the soybean meal where 0.04 ppm HP-001 was detected. In one of the three tests, soybean hulls (pods) contained 0.03 and 0.06 ppm HP-001 from treatment rates of 2.5 and 5 lbs. ai/acre.

Total residues (sum of residues converted to HP-001 and HP-002) of Metolachlor in soybean forage ranged from 0.20 to 0.36 ppm at a 2 lbs. ai/acre application rate. Total residues in soybean forage at the 3 lbs. ai/acre ranged from 0.15 to 1.01 ppm. At exaggerated rates of 4 lbs. and 6 lbs. ai/acre, total residues ranged from 0.34 to 1.76 ppm. These residue studies represented pre-harvest intervals of 30-92 days.

Total residues in soybean hay at pre-harvest intervals of 122-194 days ranged from less than 0.10 to 0.84 ppm at rates of up to 3 lbs. ai/acre. At exaggerated rates of 4 to 6 lbs. ai/acre, total residues ranged from 0.14 to 2.46 ppm.

The above residue data for soybeans allows for an adequate range of geographical variation.

Residues in or on Sorghum

Forty-five residue studies were performed in seven states representing the major sorghum growing areas. Application rates were 2 to 5 lbs. ai/acre. Analyses involved the determination of both HP-001 and HP-002 in silage stage forage, harvest fodder, and mature grain.

Residues of HP-001 in the silage stage forage (sampled at 55 to 111 days after treatment) were 0.05 to 0.56 ppm due to a rate of 2 lbs. ai/acre; less than 0.03 to 0.34 ppm due to 2.5 lbs. ai/acre; and, 0.14 to 0.51 ppm due to a rate of 5 lbs. ai/acre (two times the maximum proposed rate). Residues of HP-002 in the silage stage forage were less than 0.05 to 0.43 ppm due to a rate of 2 lbs. ai/acre; less than or exactly 0.05 to 0.11 ppm due to a rate of 2.5 lbs. ai/acre; and less than 0.05 to 0.46 ppm due to a rate of 5 lbs. ai/acre.

Samples of mature grain and harvest fodder were collected at intervals of 85 to 169 days after treatment and analyzed. Resides of HP-001 in the harvest fodder were 0.06 to 0.96 ppm due to a 2 lbs. ai/acre application rate; 0.06 to 1.90 ppm due to a 2.5 lbs. ai/acre rate; and 0.14 to 0.99 ppm due to a 5 lbs. ai/acre rate. Residues of HP-002 in the harvest fodder were less than 0.05 to 0.20 ppm due to a 2 lbs. ai/acre rate; less than 0.05 to 1.29 ppm due to a 2.5 lbs. ai/acre rate; and, 0.07 to 0.45 ppm due to a 5 lbs. ai/acre rate.

Residues of HP-001 in sorghum grain were less than 0.03 to 0.11 ppm due to the 2 lbs. ai/acre application rate; less than 0.03 to 0.18 ppm due to the 2.5 lbs. ai/acre rate; and less than 0.03 to 0.37 ppm due to the 5 lbs. ai/acre rate. No detectable residues of HP-002 (less than 0.05 ppm) were noted in sorghum grain from any application rate.

Two processing studies were performed on sorghum grain. The grain was obtained from crops treated at 2 lbs. ai/acre and harvested at intervals of 114 to 146 days after treatment. The grain had HP-001 residues of less than 0.03 to 0.09 ppm, but no HP-002 residues were detected (less than 0.05 ppm). The bran had 0.03 ppm HP-001 residues. However, no residues of HP-001 (less than 0.03 ppm) or HP-002 (less than 0.05 ppm) were detected in the flour or shorts.

These residue data are sufficient to reflect residues of Metolachlor and its metabolites in sorghum grain and its processing fractions (bran, flour, and shorts) and in sorghum forage and fodder.

Residues in or on Peanuts

Seventy-six residue studies were performed in 5 major peanut growing areas of the United States. Application rates were 3 lbs. ai/acre and 6 lbs. ai/acre. Analyses involved the determination of both HP-001 and HP-002 in peanuts, peanut hulls, peanut forage, and peanut hay. The peanuts, hulls, and hay were sampled st intervals of 128 to 159 days after treatment. The peanut forage was sampled at intervals of 56 to 69 days after treatment.

The peanuts had no detecable residues of either HP-001 (less than 0.03 ppm) or HP-002 (less than 0.05 ppm) due to the 3 lbs. ai/acre application rate. At the 6 lbs. ai/acre rate, HP-001 residues were less than 0.03 to 0.05 ppm, and HP-002 residues were less than 0.05 to 0.10 ppm.

The peanut hulls had HP-001 residues of 0.06 to 0.24 ppm and HP-002 residues of less than 0.05 to 0.45 ppm due to the 3 lbs. ai/acre application rate. Residues due to the 6 lbs. ai/acre rate were 0.07 to 0.74 ppm for HP-001 and 0.06 to 1.3 ppm for HP-002.

The peanut forage had 0.09 to 1.7 ppm HP-001 residues and 0.12 to 1.2 ppm HP-002 residues due to the 3 lbs. ai/acre application rate. Residues due to the 6 lbs. ai/acre rate were 0.12 to 3.0 ppm HP-001 and 0.14 to 1.6 ppm HP-002.

The peanut hay had 0.26 to 1.5 ppm HP-001 residues and 0.17 to 1.1 ppm HP-002 residues due to the 3 lbs. ai/acre application rate. From the 6 lbs. ai/acre rate, HP-001 residues were 0.46 to 3.0 ppm and HP-002 residues were 0.26 to 2.9 ppm.

Treated peanuts were processed to peanut cake (or, peanut meal), crude oil, refined oil, and soapstock. Processing was perfomed by either mechanical extraction or solvent extraction of the oil. The peanut cake (or meal) and the crude and refined oil had no detectable residues of HP-001 (less than 0.03 ppm) due to the 3 or 6 lbs. ai/acre rates. The soapstock had no detectable HP-001 residues due to the 3 lbs. ai/acre rate, but at the 6 lbs. ai/acre rate, the soapstock had HP-001 residues of less than 0.03 to 0.04 ppm. No detectable residues of HP-002 (less than 0.05 ppm) were noted in the crude or refined oil, or the soapstock due to either the 3 or 6 lbs. ai/acre rates. The peanut cake (or meal) had no detectable residues of HP-002 (less than 0.05 ppm) due to the 3 lbs. ai/acre rate, but at the 6 lbs. ai/acre rate, the peanut cake had HP-002 residues of less than 0.05 to 0.07 ppm.

These residue data are sufficient to reflect residues of Metolachlor and its metabolites in peanuts, peanut forage, peanut hay, and peanut by-products (meal, oil, and soapstock).

Residues in or on Potatoes

Residue data were available for the root crop, potatoes. Eighty-four residue studies were performed in seven states representing potato growing areas. Application rates were 3 lbs. ai/acre and 6 lbs. ai/acre. Analyses involved the determination of both HP-001 and HP-002 in immature (48 to 84 days after treatment) and mature (67 to 135 days after treatment) potatoes.

Residues of HP-001 in immature or mature potatoes due to the 3 lbs.

ai/acre rate were less than 0.03 to 0.05 ppm. Residues of HP-002 in immature and mature potatoes were less than 0.05 to 0.07 ppm due to the 3 lbs. ai/acre application rate. From the 6 lbs. ai/acre rate, residues of HP-001 in immature potatoes were less than 0.03 to 0.22 ppm and less than 0.03 to 0.05 ppm in mature potatoes. Residues of HP-002 were less than 0.03 to 0.28 ppm in immature potatoes and less than 0.05 to 0.06 ppm in mature potatoes.

We have concluded (see the discussion on 'Metabolism in Plants') that the absence of metabolism studies on root crops precludes an understanding of the nature of the residues in potatoes. Therefore, valid conclusions about these reported residue levels in potatoes cannot be determined.

Residues in Meat, Milk, Poultry, and Eggs

Residues in meat and milk were studied in a three-level feeding study (Mattson, 1975). In this study, eleven cows were fed unlabeled Metolachlor at levels of zero, 0.02 ppm, 1.0 ppm, and 5.0 ppm of the total diet. Milk samples were collected at zero, 1, 2, 7, 14, 21, and 28 days. Animals were sacrificed and samples of tissues taken at 14, 21, and 28 days. Only milk and tissue samples from the two highest feeding levels (1.0 and 5.0 ppm) were analyzed.

In this study, the analytical method determined "total" residues of Metolachlor, (i.e., parent compound and all metabolites yielding HP-001 and HP-002 after hydrolysis with 6N HCl). All residues in milk samples were less than the method sensitivity of 0.006 ppm for HP-001 and 0.01 ppm for HP-002. All residues in the muscle, fat, kidney, and liver were less than the method sensitivity of 0.02 ppm for HP-001 and 0.04 ppm for HP-002.

Total ^{14}C-residues (calculated as Metolachlor) were determined in the goat metobolism study where 4.7 ppm of ^{14}C-labeled Metolachlor was fed for 10 days (Roger and Cassidy, 1974a). Activity levels were equivalent to 0.01 ppm in milk, 0.003 ppm in kidney, 0.07 ppm in liver, and less than0.006 ppm in other tissues. The activity was not characterized. When ^{14}C-labeled corn biosynthesized metabolites were fed to goats, no detectable ^{14}C-residues resulted in milk or tissues (Roger and Cassidy, 1974b).

Residues in poultry and eggs were determined in a feeding study involving 112 laying hens (Mattson, 1975). The birds were fed unlabeled Metolachlor at levels of zero, 0.1, 0.5, and 2.0 ppm in the dry diet. Egg samples were taken on days 1, 3, 7, 10, 14, and 21. Birds were sacrificed after 7, 14, 21, and 28 days for tissue analysis. Only tissue and eggs samples from the two highest feeding levels (0.5 and 2.0 ppm) were analyzed. Residues as HP-001 in eggs, muscle, and fat were reported as less than 0.02 ppm. Residues of 0.02 ppm and 0.03 ppm as HP-001 were reported for the livers from birds fed at 0.5 and 2.0 ppm feeding levels, respectively. No detectable residues (less than 0.04 ppm) of HP-002 were found in eggs nor in any tissues.

From the feeding of soybean meal, hulls, and soap-stock bearing residues of 0.1 ppm, the dietary residue level could approach 0.04 ppm for cattle and 0.03 ppm for poultry. The feeding levels at which barely detectable residues were found in the feeding studies represent exaggerations of ca. 100x for cows and 25x for poultry.

A restriction against the feeding of soybean forage or hay, including the fodder or straw from the bean harvest, precludes dietary residues for poultry and cattle except for the fractions of soybeans. Although the livestock feed use of soybean fractions may lead to small residues in meat, milk, poultry, and eggs, these residues, if present, would be at levels below the sensitivity of the analytical methods.

Present Tolerances

In 1976, Metolachlor was registered for use on corn grain, and a permanent tolerance of 0.1 ppm in corn grain (except popcorn) was established for residues of Metolachlor and its metabolites pursuant to 40 CFR 180.368 (FR 41:178, 9/13/76). Since then, Metolachlor has been conditionally registered for use on soybeans, sorghum, and peanuts, 'conditional' upon the accepted fulfillment of the following Toxicology data requirements: a two-year rat chronic feeding study, a new mouse oncogenic study, a rat oncogenic evaluation, a teratology study in a species other than the rat, and a rat multi-generation reproduction study. To accompany the registered use on soybeans and the conditionally registered uses on sorghum and peanuts, permanent tolerances were established for residues of Metolachlor and its metabolites at: 1.0 ppm for corn forage and fodder; 0.1 ppm for soybeans; 2.0 ppm for soybean forage and fodder; 0.02 ppm for meat, eggs, poultry, fat, meat by-products, and milk; 0.3 ppm for sorghum grain; 2.0 ppm for sorghum forage and fodder; 0.1 ppm for peanuts; 1.0 ppm for peanut hulls; and 3.0 ppm for peanut forage and hay. The permanent tolerances for Metolachlor and its metabolites of 0.02 ppm for eggs, milk, meat, fat, and meat by-products are enforced for the following animals: cattle, goats, hogs, horses, poultry, and sheep.

DISCIPLINARY REVIEW

Residue Chemistry Profile
Tolerance Reassessment
Generic Data Gaps
Suggested Labeling

Residue Chemistry Profile

When Metolachlor was applied as a pre-emergence treatment at 2 lbs./acre to corn and soybeans, total residues later found in plants parts were higher in soybeans than in corn. In corn, the residues were primarily metabolites conjugated with polar plant molecules such as amino acids or sugars. The major pathway of metabolism appears to be conjugation with glutathione, breakage of the thioglycoside bond to form mercaptan, conjugation of mercaptan with glucuronic acid, hydrolysis of methyl ether, and conjugation of the alcohol with a neutral sugar. Metabolic pathways in soybeans were similar to those observed in corn, and pathways in peanuts and sorghum are also expected to be similar.

The metabolism of Metolachlor in animals appears to be similar to and as complex as that in plants. But whereas plants retain their metabolic products, animals eliminate their Metolachlor metabolic products almost completely. The parent compound was rapidly metabolized and almost totally eliminated in the urine and feces of goats, rats, and poultry, and no residues or only trace amounts could be detected in the tissues, kidneys, liver, blood, or milk of animals, or in the eggs, meat, or fat samples of laying chickens. The most significant residue detected was 0.02 to 0.03 ppm in the liver of chickens.

Adequate Metolachlor-specific and metabolite-specific analytical methods are available for the detection of residues in corn, soybeans, peanuts, sorghum, meat, milk, and eggs, and data were available on actual residues in these commodities. Residue data were also available for the root crop potatoes.) No detectable residues were found in corn grain, and less than 1.0 ppm were found corn fodder, forage, and stover as a result of applying as much as 6 lbs. ai/acre. Residue data for soybeans was adequate to allow for the wide range in the geographical characteristics of the U.S. soybean crop. Detectable residues in the beans, soybean meal, hulls, forage, and hay showed that an exaggerated rate of 6 lbs. ai/acre resulted in as much as 2.46 ppm in hay and 0.21 ppm in the soybeans. But residues from treatments of up to 3 lbs. ai/acre were all less than 2.0 ppm for hay and forage and 0.1 ppm for the beans. Residue data on sorghum grain, including its processing fractions, and sorghum forage and fodder, showed that application rates of 2 lbs. ai/acre resulted in combined residues which did not exceed 2.0 ppm in forage or fodder or 0.3 ppm in grain, while a rate of 5 lbs. ai/acre resulted in as much as 0.37 ppm in grain, and a rate of 2.5 lbs. ai/acre resulted in as much as 3.19 ppm in harvest fodder. Data for peanuts showed that 3 lbs. ai/acre was the maximum application rate which did not cause residues in excess of 0.1 ppm in peanuts, 1.0 ppm in peanut hulls, and 3.0 ppm in peanut forage and hay. An application rate of 6 lbs. ai/acre resulted in as much as 2.04 ppm combined residues in peanut hulls, 5.9 ppm in peanut hay, and 4.6 ppm in peanut forage. Residues at just above or below the sensitivity of the analytical method were reported for cattle meat and milk, for goat meat and milk, and for poultry eggs, meat, and

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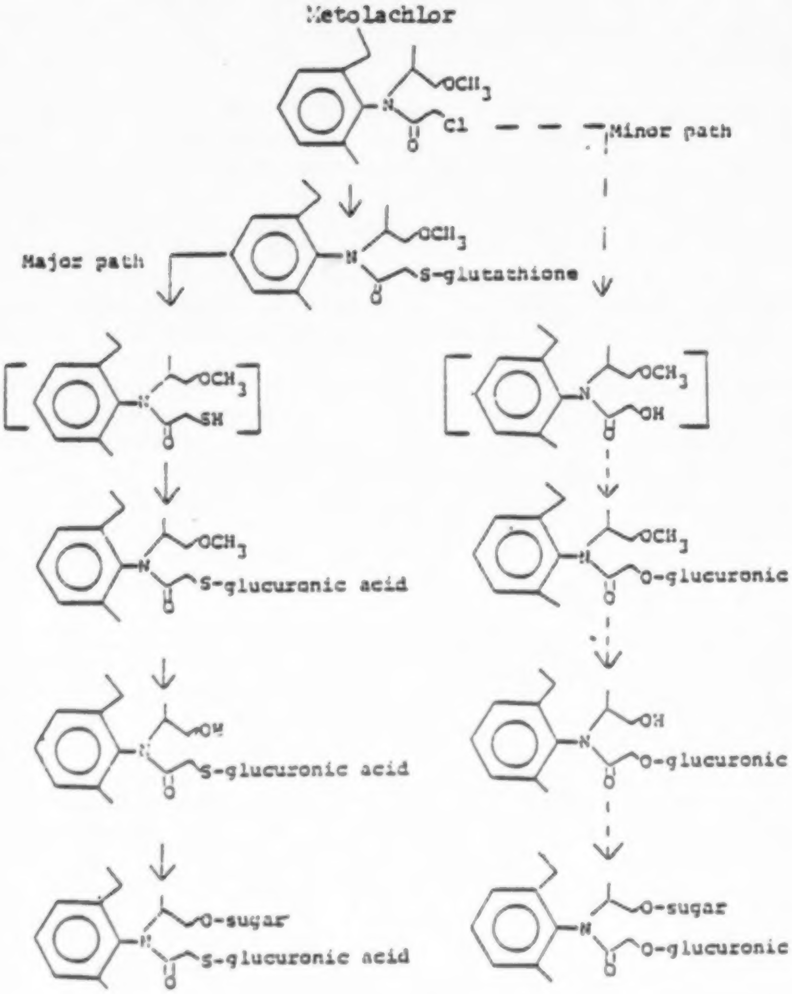
METABOLIC PATHWAYS OF METOLACHLOR
IN CORN AND SOYBEANS


Metolachlor
OCH3
N
Cl
O
Minor path
Major path
S-glutathione
SH
OH
S-glucuronic acid
O-glucuronic
O-sugar

fat. The feeding levels at which barely detectable residues were found represent exaggerations of about 100 times for cows and 25 times for poultry. Finally, the absence of metabolism studies on root crops precluded the regulatory evaluation of levels observed for potatoes.

Metolachlor has permanent tolerances of 0.1 ppm in corn grain (except popcorn), 1.0 ppm for corn forage and fodder, 0.1 ppm for soybeans, 2.0 ppm for soybean forage and fodder, 0.02 ppm for meat, eggs, poultry, fat, meat by-products, and milk, 0.3 ppm for sorghum grain, 2.0 ppm for sorghum forage and fodder, 0.1 ppm for peanuts, 1.0 ppm for peanut hulls, and 3.0 ppm for peanut forage and hay. The permanent tolerances for Metolachlor and its metabolites of 0.02 ppm for eggs, milk, meat, fat, and meat by-products are enforced for the following animals: cattle, goats, hogs, horses, poultry, and sheep.

Tolerance Reassessment

The only presently available 'no observed effect level' (NOEL) on which to base a re-assessment of Metolachlor's established tolerances is given by a six-month dietary study on dogs, which indicated a NOEL of 100 ppm (see the 'Toxicology' chapter). The following set of calculations re-assesses the acceptability of the established tolerances for Metolachlor, that is, the degree of hazard presented to the general population by dietary exposures to Metolachlor resulting from its registered end-uses.

1) The first step in the tolerance re-assessment is the calculation of a level of Metolachlor and metabolite residues which, on the basis of available animal studies, can probably be ingested by the general human population without the occurrence of toxicological effects in any individual. The only available animal study which can be used to estimate this level was a six-month feeding study on dogs, which demonstrated a 'no observed effect level' (NOEL) of 100 ppm in dogs.

   In the context of the dog study, a dietary exposure of 100 parts Metolachlor per million parts food is equivalent to 2.5 mg Metolachlor per kg of dog per day. That is, the NOEL of 100 ppm is equivalent to a NOEL of 2.5 mg/kg/day. The translation of a level which caused no toxicological effects in animals to a level safe for humans usually takes into account a safety factor of at least 100x, to allow for a 10x greater sensitivity of humans over test animals, and to allow for the possibility of an individual who is 10x more sensitive than the average person. But because of the numerous chronic data gaps for Metolachlor, a safety factor of 2000 times is recommended. Thus, the dog study allows us to calculate an 'allowable daily intake' (ADI) of

   $$2.5 \text{ mg/kg/day divided by } 2000 = 0.0013 \text{ mg/kg/day}$$

   0.0013 mg/kg/day for humans. For the average human, who weighs approximately 60 kilograms, the 'maximum permissable intake' (MPI) is

   $$0.0013 \text{ mg/kg/day} \times 60 \text{ kg} = 0.0750 \text{ mg/day}$$

   thus 0.0750 mg/day. This safe daily level of dietary exposure, the MPI, will be compared to the total residue intake permitted by the tolerances for Metolachlor.

2) The maximum total residue intake permitted by established tolerances is then calculated in three steps: (a) by multiplying the tolerance level (in mg/kg) for a particular commodity by the percentage of the total aggregate American diet supplied by that commodity ('Food Factor'); (b) then converting that value into the total mg of residue in an individual's daily diet contributed by that commodity (where the average human daily diet is taken to be 1.5 kg food); (c) and finally summing the total mg of residue in an individual's daily diet from all possible food sources. These calculations are performed in the table below for each of Metolachlor's established tolerances:

Commodity	Tolerance	Food Factor	Maximum Residue Contribution
corn (grain)	0.10 mg/kg	1.00 %	0.00150 mg/day/1.5 kg diet
soybeans	0.10	0.92	0.00138
meat, poultry	0.02	13.85	0.00415
milk, dairy	0.02	28.62	0.00858
eggs	0.02	2.77	0.00083
sorghum	0.30	0.03	0.00014
peanuts	0.10	0.36	0.00054

Total Maximum Residue Contribution = 0.01712 mg/day/1.5 kg diet

We see that the total maximum residues (TMRC) of Metolachlor and metabolites, from all potentially contaminated dietary sources, that may be ingested in 1.5 kg of food each day, is 0.0171 mg.

3) The percentage of the toxicologically-determined 'maximum permissable intake' (MPI) [from step (1) above] supplied by the 'total maximum residue contribution' (TMRC) [from step (2) above], is an indication of the degree to which the present tolerances ensure against human effects due to dietary exposure. For Metolachlor, the maximum

TMRC	divided by the	MPI	x	100 %	=	% MPI in human diet
0.0171 mg/day		0.0750 mg/day				22.82 %

possible residues in the average 1.5 kg daily diet is only 22.82 % of the level which has been determined safe for the average 60 kg person on the basis of a 2000x safety factor. This suggests that the present tolerances are more than adequate for ensuring against the potential hazards of human dietary exposure to Metolachlor. It also suggests that additional dietary sources of residues may be added to the present ones - that is, additional similar tolerances may be established for Metolachlor - without exceeding the safe dietary level (the MPI).

The established tolerances for Metolachlor on corn grain, soybeans, peanuts, sorghum, and meat, poultry, milk, and eggs have been re-assessed to be sufficient to protect against adverse human effects with a margin of safety of more than 2000x. Although the approval and establishment of tolerances requires other information, calculations also indicate that certain additional tolerances could be accommodated without exceeding the 'maximum permissable intake' for Metolachlor in the daily diet.

Generic Data Gaps

If a permanent tolerance is to be considered for Metolachlor in root crops, a root crop plant metabolism study will be needed.

Suggested Labeling

none

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ECOLOGICAL EFFECTS

TOPICAL DISCUSSIONS

Corresponding to each of the Topical Discussions listed below is the number of the sections in the 'Proposed Guidelines' of July 10, 1978 (FR Part 163) which explain the data that the Agency will require in order to assess Metolachlor's Ecological Effects.

	Guidelines Sections
Microbes	163.62-8(f) and (g)
Algae	(163.122-2, .123-2, .124-2, and .125-4)*
Aquatic Macrophytes	(163.122-2, .123-2, .124-2, and .125-4)*
Terrestrial Plants	(163.121-1, .122-1, .123-1, .124-1, and .125)*
Birds	163.70-1, .71-1, .71-2, .71-4, and .71-5
Wild Mammals	163.70-1, .71-3, and .71-5
Aquatic Invertebrates	163.70-1, .72-2, .72-4a(1), .72-5, and .72-6
Fish	163.72-1, .72-4, .72-5, and .72-6
Ecosystem Effects	163.71-5 and 163.72-6

* Subpart J of the Proposed Guidelines, which will cover phytotoxic effects, has not yet been published as final rulemaking.

Microbes

Data on the effects of pesticides on microbes are obtained from laboratory studies employing non-radioisotopic analytical techniques. These studies determine effects on either microbial functions or microbial populations. The study of effects on microbial functions constitutes a more direct approach, but some effects cannot be measured directly and population studies may be the only recourse. Studies should be conducted over a long enough period to demonstrate whether there is a temporary or long-lasting effect on microbes. Three studies were submitted for Metolachlor. Two of the studies used the population approach and one used the functional approach.

In the first population study (Houseworth, 1973a), reviewers noted variations in tabulated results, and raised questions about the aggregation, dilution, dispersal, enumeration, and identification of selected soil microorganisms (such as Bacillus, Pseudomonas, Arthrobacter, Cellulomonas, Cytophaga, Flavobacterium, Achromobacter, Aspergillus, Chaetomium, Fusarium and Penicillium). These issues will require clarification before this study can be used to support regulatory decisions.

In the other population approach study (Ercegovich, Bogus, and Buly, 1978), a diverse selection of microorganisms with 27 species representing the family

Actinomycetes and the following genera: *Bacillus, Cellulomonas, Cytophaga, Flavobacterium, Pseudomonas, Archromobacter, Aspergillus, Chaetomium, Fusarium, Penicillium,* and *Tricoderma*, were evaluated against three concentrations of Metolachlor; 5, 25, and 125 ppm. At 5 ppm, 6 of 27; at 25 ppm, 9 of 27; and at 125 ppm, 19 of 27 species were inhibited with a static (but not cidal) effect shown. At 5 ppm, 4 of 27 species had increased counts and 1 species did not show any effect at all three concentrations. Potential degraders could be estimated and 10 of 27 species could have this potential. Data for oxygen consumption, carbon dioxide evolution, nitrogen cycling, dehydrogenase activity, and phosphatase activity were not supplied. Because application rates normally used for Metolachlor are 1-3 lbs ai/A, the slight inhibitory/static effect on soil commensal populations would not be as significant as the laboratory study indicates, would be alleviated with time, and would allow populations to recover. The effect would be further minimized by reduction of the pesticide concentration by physico-chemical means, of which photolysis is a major pathway. Based on these actions, the fact that dehydrogenase or phosphatase activity data were not submitted does not invalidate the use of this study.

In a study by Ercegovich, Vallejo, and Bogus (1978), the effect of 5, 25, and 125 ppm concentrations of Metolachlor was evaluated on the soil function processes of nitrification in two soil types: Morrison sandy loam and Hagerstown silt loam. Morrison sandy loam did not show any inhibitory effects at any of the three concentrations evaluated. Hagerstown silt loam did not show any inhibitory effects at 5 or 25 ppm, but did show an inhibitory effect at 125 ppm. The rate of nitrification was inhibited for seven weeks, with a recovery starting at eight weeks and continuing until the end of the experiment (at ten weeks). Rates between the two soils varied considerably.

Though this latter study does not by itself fully explore the potential effects of Metolachlor on microbial functions (for example, effects on the degredation of cellulose, starch, and protein), it does support the data in Ercegovich, Bogus, and Buly (1978), and together these studies provide sufficient information about potential effects on naturally occurring microorganisms.

The activated sludge process used in wastewater treatment plants utilizes the metabolic degredation activity of certain microbes to break down raw sewage into a form acceptable for discharge in environmental waters. Because Metolachlor rinsate or irrigation mix may inadvertently make its way into municipal sewage systems, studies on its potential effects on wastewater treatment microorganisms is important. Not only may this cause unprocessed sewage to be released into the aquatic environment, but it may also impede the degradation of other toxics that are disposed of in sewer system drains.

A laboratory study of the effects of Metolachlor on activated sludge metabolism is not presently available for Technical Metolachlor, and this constitutes a data gap.

Algae

Studies on Metolachlor's toxicity to algae are not presently available. But because residues of Metolachlor are expected to reach the freshwater aquatic environment, if such studies were available, they would be reviewed and assessed for information on potential effects to freshwater aquatic ecology. The Agency will not presently require data on Metolachlor's effects on algae because Subpart J of the Proposed Guidelines, which will cover phytotoxic effects, has not yet been published as final rulemaking.

Aquatic Macrophytes

Studies about Metolachlor's effect on aquatic plants are not available. But because residues of Metolachlor are expected to reach the freshwater aquatic environment, if such studies were available, they would be reviewed and assessed for information on potential effects to freshwater aquatic habitats. The Agency will not presently require data on Metolachlor's effects on aquatic macrophytes because Subpart J of the Proposed Guidelines, which will cover phytotoxic effects, has not yet been published as final rulemaking.

Terrestrial Plants

Studies on the ecological effects of Metolachlor on non-target terrestrial plants are not presently available. The Agency will not now require data on Metolachlor's effects on terrestrial plants because Subpart J of the Proposed Guidelines, which will cover phytotoxic effects, has not yet been published as final rulemaking.

Efficacy tests which examine the effects of an herbicide on protected crops can often supply sufficient information to conduct an ecological effects review of phytotoxicity. Nevertheless, in accordance with present Agency policy, which requires an efficacy review for pesticides only when the chemical's intended effects has a direct impact on public health, efficacy data was not reviewed for the Metolachlor Standard.

Birds

The minimum data required for establishing the acute and subacute toxicity of Metolachlor to birds are the results from two 8-day dietary studies and one oral study with technical Metolachlor. Two types of birds - waterfowl (preferably mallard duck) and upland game (preferably bobwhite quail) are to be tested as per the specifications in FR 163.71-1 and 163.71-2.

Five studies of technical Metolachlor's effects on birds were available for evaluation, all performed by Fink: two studies performed in 1974, one in 1976, and two in 1978.

Fink's 1976 study reported data on the effects of single oral doses of technical Metolachlor to avian wildlife: the acute LD-50 for mallards (Anas platyrhynchos) was 4640 (3000-7200, 95% confidence limits) mg/kg, indicating that Metolachlor is practically non-toxic, acutely, to waterfowl. But due to deviations from recommended protocols, such as discrepancies in body weights, this study is unacceptable for use in the regulatory process. An avian single dose oral LD-50 determination is thus a data gap for Metolachlor.

Acceptable data on the dietary LC-50 of technical Metolachlor for avian wildlife are reported on the mallard (*Anas platyrhynchos*) (Fink, 1974a), and the bobwhite quail (*Colinus virginianus*) (Fink, 1974b). The 5-day dietary LC-50 (with 3 days observation) for both species was greater than 10,000 ppm, indicating that technical Metolachlor is practically non-toxic, subacutely, to upland gamebirds and waterfowl. These two studies meet the guidelines requirement for avain dietary testing.

Because, as was seen in the Environmental Fate chapter, technical Metolachlor is persistent under certain conditions and is stored in plant and rotational crop tissue, information on avian reproduction effects was also needed. In 1978, Fink performed two studies of technical Metolachlor's effects on avian reproduction.

The first reproduction study (Fink, 1978a) tested the bobwhite quail with seventeen (17) weeks of dietary exposure during mating, egg laying, and egg hatching. In comparison with the controls, bobwhite quail exposed to 10, 300, and 1000 ppm Technical Metolachlor for 17 weeks produced significantly fewer chicks surviving to 14 days. (See table 1.)

table 1

Summary of Reproductive Success of Quail Exposed to Metolachlor for 16 Weeks

Pesticide Concentration	Percent Survival[1]	Chi-Square[2]	DF	Significance Level
Control	58.8%	-	-	-
10 ppm	47.0%	22.35	1	>0.001
300 ppm	37.0%	62.4	1	>0.001
1000 ppm	41.5%	44.5	1	>0.001

[1] The number of chicks surviving to age 14 days expressed as a percentage of the eggs laid.

[2] Chisquare calculated by 2x2 Contingency Table analysis of treatment versus control group survival.

Although the subacute dietary LC-50 to quail was shown to be greater than 10,000 ppm, there appeared to be a dose response for mortality among the females subjected to a dietary exposure for seventeen weeks, as seen in table 2 below.

table 2

Bobwhite Quail Dosed with Metolachlor for 17 Weeks

dietary dose	number of female deaths
0 ppm (control)	2
10 ppm	1
300 ppm	4
1000 ppm	7

The other reproduction study (Fink, 1978b) was performed on the mallard duck, using the same dietary dose levels for the same 17 weeks. In comparison with the controls, mallard ducks exposed to 10 and 1000 ppm Technical Metolachlor for 17 weeks produced significantly fewer chicks surviving to 14 days. (See table 3 below.)

table 3
Summary of Reproductive Success of Mallards Exposed to Metolachlor for 16 Weeks

Pesticide Concentration	Percent Survival[1]	Chi-Square[2]	DF	Significance Level
Control	57.0%	-	-	-
10 ppm	48.0%	11.29	1	>0.001
300 ppm	57.6%	0.053	1	NS
1000 ppm	51.0%	5.26	1	>0.025

[1] The number of ducklings surviving to age 14 days expressed as a percentage of the eggs laid.

[2] Chisquare calculated by 2x2 Contingency Table analysis of treatment versus control group survival.

But the female ducks suffered no dose-related mortality, as seen in table 4 below. The one duck mortality at 300 ppm was attributed to an impacted oviduct, rather than to a chemical-related effect. These two 1978 studies by Fink are sufficient to satisfy the guideline requirements for avian reproductive testing.

table 4
Mallard Duck Dosed with Metolachlor for 17 Weeks

dietary dose	number of female deaths
0 ppm (control)	0
10 ppm	0
300 ppm	1
1000 ppm	0

In summary, all guideline data requirements for avian effects are fulfilled except the acute oral LD-50, which is presently a data gap for Metolachlor. On the basis of available data, this Standard will not require precautionary labeling addressing toxicity to birds.

Wild Mammals

Mammalian toxicity data are not needed for Metolachlor because the data on laboratory animals reviewed in the Toxicology Chapter are generally sufficient for an estimation of toxicity to wild mammals. Based on the data in Metolachlor's Toxicology review, there does not appear to be any unusual toxicity, and therefore, no special precautions need be recommended.

Aquatic Invertebrates

The minimum data required for an outdoor use pesticide to establish its acute toxicity to aquatic invertebrates is the result of one 48 or 96 hour study using the technical, as described in FR 163.72-2. One such study by Vilkas (1976) was available for Metolachlor. Vilkas exposed water fleas (Daphnia magna Straus) to technical Metolachlor for 48 hours. The 48-hour no-effect level was 5.6 ppm. The 48-hour LC-50 at 95% confidence limits is 25.1 (21.6-29.2) ppm. These data satisfy the guidelines requirement for aquatic invertebrate testing and are sufficient to characterize Metolachlor as being slightly toxic to aquatic invertebrates.

Fish

A determination of the 96-hour LC-50 of the technical compound for one cold-water fish species (preferably rainbow trout) and one warm-water fish species (preferably bluegill) is required for all outdoor use pesticides. The acute toxicity of technical Metolachlor to freshwater fish was reported in two studies conducted by Buccafusco (1978a, 1978b), one study by Sachsse and Ullman (1974), and one study by Dionne (1978). As shown in the following table, some of these tests could be used to satisfy Agency data requirements, while others, although they also offered useful information, were not directly applicable to the data requirements.

Species	96 hr LC-50	Author	Date	Satisfies EPA Data Requirements
Bluegill sunfish	10.0 ppm	Buccafusco	1978	yes
Rainbow trout	3.9 ppm	Buccafusco	1978	yes
Fathead minnow	11.0 ppm (static)	Dionne	1978	no
Fathead minnow	9.2 ppm (flow)	Dionne	1978	no
Crucian Carp	4.9 ppm	Sachsse	1974	no
Channel Catfish	4.9 ppm	Sachsse	1974	no
Guppy	8.6 ppm	Sachsse	1974	no

These tests provide sufficient information to characterize Metolachlor as moderately toxic to both warm-water and cold-water fish. The guidelines requirement for LC-50's for both types of fish has been satisified.

As was seen in the Environmental Fate chapter, Metolachlor is resistant to hydrolysis and metabolism in soil, and has a tendency to leach. With this potential for residues to migrate to freshwater aquatic habitats, a chronic fish study, as described in FR 163.72-4, was required.

One such study was available. It was performed by Dionne (1978), and tested the effects of 97.4% Metolachlor on the reproduction of the Fathead minnow (Pimephales promelas). When the minnows were exposed to a measured concentration of $>$ 1.60 ppm, significantly ($p=0.05$) fewer first and second generation fry survived. The majority of mortalities occurred during the 4th week of exposure. The 'maximum acceptable toxicant concentration' (MATC), the concentration below which no effects were observed, was reported to be between 0.78 and 1.60 ppm.

The ratio of the MATC to the LC-50 for the same species is called the 'application factor' (AF). Because the AF is essentially a property of the pesticide (i.e., its acute versus its chronic mode of action), the AF can be used to calculate an estimated MATC for any fish species for which one knows the 96-hour LC-50. Dividing the minnow MATC values of 0.78 and 1.60 by the 96-

hour flow-through LC-50 for minnows (9.2 ppm), the application factor (AF) for Metolachlor was calculated to be between 0.08 and 0.17. This AF for Metolachlor was then used to calculate an estimation of the MATC for other fish species:

species	96-hour LC-50	estimated max acceptable tox conc (MATC)
Bluegill sunfish	10.0 ppm	0.8 ppm to 1.7 ppm
Rainbow trout	3.9 ppm	0.3 ppm to 0.7 ppm
Crucian Carp	4.9 ppm	0.4 ppm to 0.8 ppm
Channel Catfish	4.9 ppm	0.4 ppm to 0.8 ppm
Guppy	8.6 ppm	0.7 ppm to 1.5 ppm

The 1978 minnow reproduction study by Dionne satisfies the requirement for a study of technical Metolachlor's chronic effects on a freshwater fish species, and allows an estimation of potentially hazardous residue levels for several other species.

On the basis of available acute and chronic toxicity information, which indicates a moderate toxicity to fish, the following precautionary labeling appears appropriate. For the technical: "Do not discharge into lakes, streams, ponds, or public waters unless in accordance with an NPDES permit." And for the emulsifiable concentrate: "Avoid direct application to any body of water. Do not apply where runoff is likely to occur. Do not contaminate water by cleaning of equipment or disposal of wastes."

Ecosystem Effects

The need for studies of ecosystem effects, including such field studies as those described in FR 163.71-5 and 163.72-6, cannot presently be determined because the available laboratory data have not yet been correlated with an estimation of potential 'environmental concentrations'. If fate or monitoring information suggest the potential for chronic adverse effects to fish or birds, the Agency will consider imposing a requirement for field data.

DISCIPLINARY REVIEW

Ecological Effects Profile
Ecological Effects Hazard Assessment
Generic Data Gaps
Suggested Labeling

Ecological Effects Profile

Technical Metolachlor: Scientifically sound data on the toxicity of Metolachlor to wildlife are available on a wide range of non-target organisms. Fish appear to be the most sensitive class tested.

A diverse selection of soil microorganisms were evaluated against three concentrations of Metolachlor: 5, 25, and 150 ppm. Only static, not cidal, effects were noted (Ercegovich, Bogus, and Buly, 1978). Another study using the same concentrations showed no effects on nitrification at the two lower levels, and only temporary inhibition at the high level (Ercegovich, Vallejo, and Bogus, 1978). Effects on wastewater treatment microorganisms have not yet been investigated.

Subacute dietary studies on the mallard duck and bobwhite quail, as well as an acute oral test on the mallard duck, indicate that Metolachlor is practically non-toxic to birds. However, in reproduction studies, Bobwhite Quail and Mallard ducks fed 10 ppm in their diet for 17 weeks experienced significant ($p<0.001$) reproductive impairment: fewer chicks surviving to 14 days. Ten parts per million was the lowest of three concentrations tested, and therefore a 'no observed effect level' has not been established.

Based on data reviewed in the Toxicology chapter, Metolachlor appears to present a low toxicity to wild mammals. Data on the acute toxicity of Metolachlor to the water flea show that the herbicide is slightly toxic to aquatic invertebrates, with a 48-hour LC-50 of 25.1 ppm.

Fish were clearly the most acutely sensitive of the organisms tested. The cold-water fish Rainbow trout had an LC-50 of 3.9 ppm, and the warm-water Bluegill sunfish had an LC-50 of 10.0 ppm, indicating that Metolachlor is likely to be moderately toxic to both cold and warm water species. Indeed, tests on additional warmwater species, including the Crucian carp, Channel catfish, Guppy, and Fathead minnow showed comparable LC-50's ranging between 4.9 and 11.0 ppm. In a fish reproduction study on the Fathead minnow, fry of both the F_0 and F_1 generations suffered significant mortality at levels greater than 1.6 ppm. The MATC was estimated for the various fish species, and ranged from 0.3 to 1.7 ppm.

Emulsifiable Concentrate Metolachlor: Information on the toxicity of the Emulsifiable Concentrate to non-target wildlife organisms is effectively supplied by the studies on the Technical chemical.

Ecological Effects Hazard Assessment

Technical Metolachlor: For non-target organisms in the proximity of Technical Metolachlor manufacture, storage, shipping, or disposal, intentional discharges of the chemical into the environment, such as by the disposal or drainage of effluent, as well as unintentional discharges, such as by spillage or fire, could result in fish and wildlife exposure. Though unintentional discharges could result in a risk to fish and birds in the contaminated area, the Agency does not perceive unintentional discharges to be any more likely with Technical Metolachlor than with any other technical chemical. As concerns the disposal of wastes or factory effluent, Ecological Effects data are available to EPA officials responsible for issuing a discharge permit should one become necessary, and to EPA officials responsible for regulating the handling of hazardous wastes.

Emulsifiable Concentrate: As was pointed out in the Exposure Profile in the Environmental Fate chapter, because of the relative stability of Metolachlor to hydrolysis, its high mobility in the terrestrial environment, and its potential resistance to metabolic degradation, it is anticipated that the spraying of Metolachlor on certain terrains and soil types, and in certain types of weather, may result in the contamination of aquatic sites adjacent to treated fields. It is possible that fish can be exposed to levels of Metolachlor that would cause significant mortality to fry, although the presently available exposure information does not lead the Agency to suspect significant acute effects on freshwater fish.

Other non-target organisms of potential concern include microbes, non-target plants, soil and surface invertebrates, mammals, and birds. Soil microbes and the nitrification process do not appear to be threatened, and mammalian wildlife do not appear threatened by acute effects. Data are not presently available on toxicity to non-target plants nor to soil and surface invertebrates. Metolachlor's resistance to hydrolysis and metabolism, and the possibility of non-target plant uptake, suggest that birds may be exposed to residues in non-sensitive weeds, crops, or soil organisms from the pre-emergent application of Metolachlor to soil. (If Metolachlor is applied post-emergent or to non-tilled fields, a higher dietary exposure would be expected to occur to birds.) Because of Metolachlor's low acute toxicity to birds, the acute risk to birds is minimal. However, as concerns reproductive effects to birds, data have indicated reproductive effects at 10 ppm dietary exposure. The presently available exposure information is not sufficient to conclude that a harmful exposure level will occur in Metolachlor treated fields.

Generic Data Gaps

The following are gaps in the Ecological Effects data base which will be used to support registrations under this Metolachlor Standard. After each gap is listed the section in the Proposed Guidelines of July 10, 1978 (FR Part 163) which describes that type of test and when it is required. The following studies would test the Technical in order to assess the hazard associated with the use of the Emulsifiable Concentrates.

1)	Activated sludge metabolism study.	163.62-8(g)
2)	The avian acute oral LD-50 for one species of waterfowl (preferably the mallard) or one species of upland game bird (preferably the bobwhite quail). The species must be one of those for which an LC-50 was determined under FR 163.71-2 (see the discussion on 'Birds').	163.71-1

Suggested Labeling

For Technical Metolachlor:

"Do not discharge into lakes, streams, ponds, or public waters unless in accordance with an NPDES permit. For guidance, contact your regional office of EPA."

For Emulsifiable Concentrate Metolachlor:

"Avoid direct application to any body of water. Do not apply where runoff is likely to occur. Do not contaminate water by cleaning of equipment or disposal of wastes. Do not apply when weather conditions favor drift from target area."

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REGULATORY RATIONALE

TECHNICAL METOLACHLOR

The risks which determine the conditions of a technical chemical's registrability are those risks which arise in handling, storing, shipping, re-formulating, and disposing of it - that is, in the various aspects of its disposition as a manufacturing-use chemical. Technical Metolachlor, at least ninety percent the pure compound, is an off-white, odorless liquid, soluble in water, and miscible with several organic solvents.

The Delimitation of Risks to Humans

To review our Toxicology findings, Technical Metolachlor's acute toxicity to humans appears to be mild: it has a low acute oral toxicity, it is not readily absorbed by the skin, it has a very low inhalation toxicity, and no eye irritation effects are observable. The only significant short-term effect is skin sensitization. Once an exposure occurs, Metolachlor is rapidly metabolized and excreted. Although the available chronic effects studies were not sufficient to satisfy all the Agency's requirements for such testing, the data that were available showed no evidence of general chronic, teratogenic, fetotoxic, oncogenic, or mutagenic effects.

The Exposure Profile pointed out that for persons involved in the handling, storage, shipment, or re-formulation of Technical Metolachlor, there is little likelihood of oral exposure, and because of the low vapor pressure of the viscous liquid, there is also little chance of inhalation exposure. The most likely human exposure is a repeated dermal exposure, and occasionally, by accident, an occular exposure.

In sum, the acute risks of handling the presently registered Technical Metolachlor are minimal, and the currently available studies show no evidence of general chronic, oncogenic, mutagenic, fetotoxic, or teratogenic effects due to Metolachlor. Available studies only suggest a potential dermal sensitization problem for factory, transport, or re-formulation workers.

For the professional handling of a manufacturing-use chemical by factory, transport, or re-formulation workers, acute risks higher than those found for Technical Metolachlor are normally acceptable; because the Agency expects members of such occupations to be responsive to a chemical's accompanying label precautions. However, because it is evidently possible to manufacture a Technical Metolachlor with a mild acute toxicity, the Agency should only register Technical Metolachlor products that fall into 'Toxicity Categories' III or IV for each of the five acute tests: acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, and primary dermal irritation. Technical Metolachlor products that fall into numerically lower 'Toxicity Categories' are likely to be substantially different in either impurities or inerts from the chemical on which this Standard is based, and so a proposal to amend the Standard should accompany the application for their registration.

The Agency considers the dermal sensitization risk to be acceptable in the case of Technical Metolachlor because two reasonable regulatory actions are available for helping to preclude repeated dermal exposures: a label warning that the chemical "May cause skin sensitization" which will alert handlers to the possibility of the effect; and a label direction to "Wear protective clothing (coveralls and gloves) while handling or using this product". Unless the absence of dermal sensitization effects can be demonstrated by the appropriate toxicology study, these two requirements should be applied to the registration of any Technical Metolachlor product.

Because the most likely route of long-term exposure to a Technical Metolachlor is by repeated dermal contact, the above actions which help limit dermal exposures also serve to render more acceptable the potential for the as-yet-undetermined risk of chronic effects, at least until adequate long-term studies have been completed.

The Delimitation of Risks to Wildlife

To review our Ecological Effects findings, the available wildlife studies suggested several potential hazards for wildlife. Though the toxicity of Technical Metolachlor to birds was shown to be low in one dietary LC-50 test, a several month dietary exposure of 300 ppm was shown to produce reproductive effects in upland game birds. Fish were the most sensitive species tested, with relatively low LC-50's and a high mortality for fry in the presence of concentrations less than 2 ppm. Aquatic invertebrates have a lesser, though still significant, sensitivity.

As stated in our Exposure Profile, for wildlife in the proximity of Technical Metolachlor manufacture, handling, storage, shipping, re-formulation, or disposal, intentional discharges of the chemical into the environment, such as by disposal or drainage, as well as unintentional discharges, such as by spillage or fire, could conceivably result in wildlife exposures. But the pathway of exposure which is the most direct concern is the discharge of effluent or the disposal of Metolachlor wastes into freshwater aquatic habitats. The organisms that may be exposed by route of freshwater aquatic discharge are fish, aquatic invertebrates, and, because of plant uptake, local avian or mammalian herbivores.

Thus, if the Technical chemical or effluent from its manufacture or re-formulation were disposed of or allowed to drain into freshwater aquatic habitats, the stability of the Metolachlor compound to hydrolysis and its potential resistance to metabolic degredation, together with its moderate acute and serious chronic toxicity for fresh water fish and their fry, indicate a potential long-term risk for fish. Further, birds continually feeding on contaminated leaves or seeds could conceivably suffer reproductive effects, and aquatic invertebrates, integral to the watershed ecology, could possibly suffer a small population reduction. The suggested label precaution, "Do not discharge into lakes, streams, ponds, or public waters unless in accordance with an NPDES permit" is therefore necessary to help control contamination of the aquatic environment.

As concerns storage and disposal, it should be noted that soil injection, landspreading, and any unauthorized land disposal would not be acceptable for Technical Metolachlor because of its demonstrated mobility in soil and resistance to metabolic degradation. Metolachlor's stability to extremes of pH preclude acid or alkalai hydrolysis as a technique for disposal or container decontamination. Further, data are not presently available to demonstrate the effectiveness or safety of incineration or open burning, nor the degree of potential damage to activated sludge water treatment processes caused by disposal into a sewage system. Thus the only disposal practice that the Agency can recommend at this time is to place Technical Metolachlor in a landfill disposal site approved for pesticides.

Until the risks, particularly for fish and birds, are quantified by the comparison of toxic concentrations with anticipated 'environmental concentrations' resulting from measured applications to use sites, the potential for hazard to wildlife cannot be quantified. Nevertheless, barring a severe concentrated spill, and providing that discharge and disposal practices are appropriately controlled, the Agency does not perceive an imminent hazard to wildlife from the handling or manufacturing use of Technical Metolachlor. Until these risks are quantified, the Agency should presume that as concerns Ecological Effects, a Technical Metolachlor product will be registrable if it bears the following warnings:

Under 'hazards to wildlife': "Do not discharge into lakes, streams, ponds, or public waters, unless in accordance with an NPDES permit. For guidance, contact your Regional Office of EPA." Under 'storage and disposal' directions: "Open dumping or open burning is prohibited. Thoroughly clean containers or tanks before re-use, or re-seal and offer for recycling or reconditioning. Pesticide or rinsate that cannot be used, recycled, or chemically reprocessed, and tanks or other containers that cannot be re-used or recycled should be disposed of in a landfill approved for pesticides. Consult federal, state, or local disposal authorities for approved alternative procedures."

Section 162.11(a) of 40 CFR states that the Agency shall presume against the registration of a pesticide product which meets or exceeds certain specific risk criteria set forth therein. Because the available data on potential effects to man or the environment do not indicate that any of these risk criteria would be met or exceeded for a Technical Metolachlor which meets all the 'standards' suggested above, the Agency shall presume that such Technical Metolachlor is registerable for sale, distribution, and re-formulation in the United States.

EMULSIFIABLE CONCENTRATES of METOLACHLOR

This Standard will presently only cover 'emulsifiable concentrate' type formulations of Metolachlor, because the hazards due to other formulation types such as granulars or dusts, and the significantly different application methods they would require, are not adequately considered by the data available on the presently registered formulations. Additional data pertaining to the product chemistry, environmental fate, toxicology, residue chemistry, and ecological effects of new formulation types and their application methods would be needed to evaluate the registrability of such products.

Emulsifiable Concentrate formulations containing Metolachlor alone are appropriate for the control of weeds in non-domestic, outdoor, terrestrial food-crop fields. When not 'tank mixed' with other herbicides, the Emulsifiable Concentrates should be applied by conventional ground spray or through center pivot irrigation systems before, during, or after planting, but always before the emergence of the crop seedlings. The applications must be pre-emergence because residue data are not available to show that tolerances will not be exceeded by post-emergence applications, and because the ecological effects of a post-harvest application have not been determined, particularly for birds.

The establishment of tolerances for agricultural-use pesticides requires certain residue chemistry data. Occasionally, sufficient residue chemistry data are available for several crops within a crop grouping (e.g., 'grain crops', 'leafy vegetables', or 'root crop vegetables') so that the Agency can establish a tolerance for other crops in the grouping without requiring additional data. For Metolachlor, however, the presently available residue data are only sufficient to support tolerances for, and thereby enable the use of Emulsifiable Concentrate Metolachlor on: corn grown for grain (excluding popcorn), soybeans, (Concep-treated) grain sorghum, and peanuts. Presently available residue data show that Metolachlor Emulsifiable Concentrate can be applied pre-emergence to corn fields at a rate of up to 6 lbs. ai/acre, to soybean fields at a rate of up to 3 lbs. ai/acre, to grain sorghum fields at rates of up to 2-1/2 lbs. ai/acre, and to peanuts at up to 3 lbs. ai/acre, without exceeding the established tolerances.

If the crop treated with the Emulsifiable Concentrate is lost, it may be replanted immediately with corn, soybeans, peanuts, or (Concep-treated) grain sorghum without a second treatment.

The recommended rotational crop restriction (conditional upon an agreement to generate the required data as specified) is as follows: Small grains may be planted 4-1/2 months following treatment. Field corn (except fresh corn and popcorn), cotton, soybeans, peanuts, sorghum, root crops, and small grains may be planted in the spring following treatment. Do not graze or feed forage or fodder from cotton or small grains to livestock. All other rotational crops may be planted 18 months after application.

The Delimitation of Risks to Humans

It may be recalled from our Toxicology review that the presently registered Emulsifiable Concentrate formulations of Metolachlor have some potential for serious acute effects. The eight pounds per gallon formulation could produce severe irritation and burns on contact. The six pounds per gallon formulation can cause serious eye irritation, including irreversible corneal opacity. Like the active ingredient, any Emulsifiable Concentrate may produce skin sensitization with repeated exposures.

The Exposure Profile determined that for an outdoor agricultural ground spray, there is a possibility of dermal and eye exposure from the splashing that may occur while diluting and tank mixing, and in the loading of spray equipment. If an Emulsifiable Concentrate has a high vapor pressure, as do most products with organic solvents, an unprotected mixer or diluter who is handling an open container without adequate ventilation may be exposed to fumes. Also of concern are the spray droplets generated by the application of a ground-sprayed agricultural pesticide, which could result in an inhalation exposure for applicators and other agricultural workers who may be in the proximity of the spraying. Chronic dietary exposures for the general population are expected to occur at finite levels, due to residues on food (and in animal products from livestock fed Metolachlor-treated plant parts) which will be less than the established tolerances.

The Agency concludes that there is presently no evidence of general chronic, teratogenic, fetotoxic, oncogenic, or mutagenic effects due to end-use of Metolachlor. Known chronic dietary hazards for the general population were estimated to be avoidable at exposures less than 0.0750 mg per day. But there may be acute risks involved in the end-use of Emulsifiable Concentrate formulations. The acute risks to humans caused by the handling of these Emulsifiable Concentrate formulations consist primarily in the potential for skin and eye burns from accidental splashing, the potential for skin sensitization from repeated dermal contact, the danger of fume inhalation from mixing or loading in a poorly ventilated area, and the danger of spray inhalation near the point of ground spray application. Except for the skin sensitization hazard, the severity of these hazards from the use of a particular formulation depends upon its acute toxicity and irritation categories. The sensitization hazard depends directly upon the concentration of the active ingredient.

First we will consider the acceptability of the various acute risks.

As concerns acute oral toxicity, because Metolachlor is not intended for domestic use, and is not mixed with seeds or foodstuffs before application, there is very little chance of accidental oral exposure, and the Agency should accept Metolachlor formulations with an acute oral toxicity as high as Category II. A Category I would not be acceptable unless the formulation were classified for restricted use by certified applicators.

As concerns acute dermal toxicity, because even with appropriate label precautions there is still a reasonable chance for occasional accidental dermal exposures in mixing, diluting, loading, or spraying, the Agency should not accept a Metolachlor formulation with an acute dermal toxicity higher than Category III.

As concerns acute inhalation toxicity, although Metolachlor is an outdoor use pesticide and is commonly mixed, diluted, and loaded outdoors, because most Emulsifiable Concentrates have a high volatility, a high inhalation exposure could even occasionally occur outdoors. The actual spraying could also result in inhalation exposures for those nearby. Nevertheless, because the loading and mixing do commonly occur outdoors, because the spraying is limited to ground spraying, and because the accompanying warning "Do not breathe vapors" would be reasonably effective with even untrained applicators, a Category II inhalation toxicity should be acceptable. A formulation with a Category I inhalation toxicity, however, would require some protective apparatus, and without restricting the chemical to use by trained applicators, the Agency cannot be assured that such equipment would be consistently used. An additional limit that will not affect efficacy can be put on the exposure to vapors by limiting the physical/chemical property 'vapor pressure' to less than 1.0 mm Hg. The Agency will thus find acceptable a Metolachlor formulation with an acute inhalation toxicity as high but no higher than a Category II, and a vapor pressure between 0.05 and 1.0 mm Hg.

With the above limitations on the dermal and inhalation hazards, the Agency does not see the need to prescibe a re-entry interval for Metolachlor. Nevertheless, users should be aware that the "application of a pesticide in such a manner as to directly or through drift expose workers or other persons except those knowingly involved in the application" is expressly prohibited under 40 CFR 170.3.

As concerns primary eye irritation, the classification guidelines suggest that any Category I toxicity rating should imply a restriction of the product's use to certified applicators, unless some aspect of "formulation, packaging, or method of use of the product (which) can reasonably be expected to eliminate the route of exposure" is available and is likely to be effective [162.11 (c)(2)]. In the case of Metolachlor as an agricultural-use crop field spray, the requirement to "Wear goggles or face shield when handling" which accompanies a Category I formulation can be expected to be complied with by even untrained agricultural workers or applicators, and it may be assumed that such protective equipment as goggles are commonly available to pesticide applicators. This assurance allows the Agency to accept a Metolachlor formulation with a primary eye irritation as high as Category I.

As concerns primary dermal irritation, because of the likelihood of accidental dermal exposures, the Agency should not accept a formulation with a dermal irritation higher than Category II. (Category II is acceptable for dermal irritation, but not for dermal toxicity, because some high concentration accidental dermal exposures are certain to occur, and a high exposure to a Category II dermal toxicity solution brings the user too close to a risk of whole body poisoning, including death, while a Category II dermal irritation could at worst result in local dermal injury.) The Agency can further delimit the risk of dermal irritation, without affecting efficacy, by limiting the physical/chemical property 'pH' to the relatively neutral range of pH 6 to pH 8.

The Agency considers the dermal sensitization risk to be acceptable in the case of Emulsifiable Concentrates of Metolachlor because two reasonable regulatory actions are available for helping to preclude repeated dermal exposures: a label warning that "The active ingredient, metolachlor, may cause skin sensitization", which will alert handlers to the possibility of the effect; and label directions to "Wear gloves and protective clothing when handling", "Wash thoroughly after handling", and "Remove and wash contaminated clothing before re-use". Even though applicators and agricultural workers who may come in contact with the chemical might be untrained in the handling of pesticide chemicals, the Agency can reasonably assume that the simple and unencumbering direction to wear gloves or other protective clothing will be obeyed most of the time. Even if, as stated above, occasional accidental dermal exposures are highly likely, only a continous series of repeated exposure could lead to dermal sensitization.

Three additional physical/chemical properties of concern for their potential health effects are flammability, explosiveness, and corrosiveness. Because Emulsifiable Concentrate Metolachlor will be handled by untrained applicators and is likely to be used or mixed near combustion engines and other machinery, it should not be "flammable" by Agency standards, which means that its flashpoint should be above 80°F. Because the solvents, however, are likely to bring the flashpoint below 150°F, users should be warned: "Do not use or store near heat or open flame" in both the 'Precautionary Statements' and 'Storage and Disposal' sections of the label. Second, because it would require special training for safe handling, no Metolachlor Emulsifiable Concentrate should be explosive or shock sensitive. Third, a corrosive pesticide might burn though application tanks or storage containers, potentially resulting in harmful skin or eye exposures. But a slight corrosiveness to steel or tin is acceptable if the warning "Do not store in unlined containers or tanks" appears in both the 'Precautionary Statements' and 'Storage and Disposal' sections of the label.

Finally, because without protective clothing the most likely route of long-term exposure for applicators is the dermal route, the above actions which help limit dermal exposures also serve to render more acceptable the potential for the as-yet-undetermined risks of chronic effects, at least until adequate long-term studies have been completed. The known chronic risks of a dietary exposure for the general public are limited by the fact that residues resulting from acceptable use patterns will not exceed established tolerances for the crops to which the formulations are applied and for products from animals which are fed these crops. Because the chronic effects data base is not yet complete, the Agency will presently consider additional food uses for Metolachlor on an incremental risk and benefits assessment basis. The established tolerances provide a more than 2000 fold safety factor between the highest potential human dietary exposure and the "no observed effect level" from a valid six-month feeding study on dogs.

The Delimitation of Risks to Wildlife

The potential effects to wildlife due to Metolachlor exposures resulting from the use of the formulations are estimated in toxicity studies on the Technical. To review our Ecological Effects findings for the Technical, the available wildlife studies suggested several potential hazards for wildlife. Though the toxicity of Technical Metolachlor to birds was shown to be low in one dietary LC-50 test, a several month dietary exposure of 10 ppm was shown to produce reproductive effects in upland game birds. Fish were the most sensitive species tested, with relatively low LC-50's and a high mortality for fry in the presence of concentrations less than 2 ppm. Aquatic invertebrates have a lesser, though still significant, sensitivity to Metolachlor.

As stated in our Exposure Profile, several aspects of Metolachlor's fate, including its tendency to leach or runoff, its stability to hydrolysis, and its resistance to microbial degradation, combine to suggest that the end-use application of Metolachlor formulations could contaminate surface and groundwater, thereby exposing fish, freshwater plants and animals, animals which drink the contaminated water, or carnivores which feed on the contaminated fish. Further, because of Metolachlor's demonstrated uptake by rotational crops, it may be assumed that some aquatic or terrestrial plants may either suffer phytotoxic exposures or pass Metolachlor residues on to herbivores, including birds.

Thus, several concerns about wildlife risks arise from the suspicion that Metolachlor residues will migrate to and persist in aquatic habitats. The most notable of these potential, but as yet unquantified, risks is that to the fry of freshwater fish. Lesser but potentially serious risks may exist for adult fish, nesting herbivorous birds, or aquatic invertebrates, the last of which can be integral to the ecology of terrestrial watersheds.

Until the Agency compares toxic concentrations with the as yet undetermined 'environmental concentrations' resulting from measured applications to use sites, the potential for hazard cannot be quantified. But unless the formulated pesticide is directly applied to or disposed of into water, heavily applied in an area of hilly terrain with soils of a high organic content, or applied when weather conditions favor drift to aquatic sites, the Agency does not forsee an immanent risk to wildlife from the routine use of Metolachlor formulations. Thus, the Agency considers these as yet unquantified risks to be temporarily acceptable, at least until a quantification becomes possible, if the labels for Metolachlor formulations present the following statements under 'hazards to wildlife': "Avoid direct application to any body of water. Do not apply where runoff is likely to occur. Do not contaminate water by cleaning of equipment or disposal of wastes. Do not apply when weather conditions favor drift from areas treated."

As with the Technical, disposal practices involving soil injection, landspreading, hydrolysis, incineration, open burning, or discharge into a sewage system are not supported by the current data. Disposal should thus be limited to landfill disposal sites approved for pesticides: "Open dumping or open burning is prohibited. Do not re-use empty container; triple rinse or equivalent. Pesticide or rinsate that cannot be used, recycled, or chemically reprocessed, and triple-rinsed containers with their rinsate, should be disposed of in a landfill approved for pesticides. Consult federal, state, or local disposal authorities for approved alternative procedures."

Section 162.11(c) of 40 CFR states that the Agency may classify for 'general use', that is, for purchase and use by any member of the general public, any end-use pesticide product which meets certain specific criteria set forth therein, or else has a formulation, package, or method of use which can reasonably be expected to eliminate the route of exposure for each hazard which exceeds a criterion [162.11 (c)(2)]. The available data on potential effects to man and the environment show that all of these criteria, except for eye irritation, would be met for an Emulsifiable Concentrate Metolachlor which was in accord with all the 'Standards' suggested in the above discussions; and eye exposure can be effectively eliminated by the requirement to "Wear goggles or face shield when handling". An Emulsifiable Concentrate Metolachlor which meets all the Standards suggested in the above discussions is therefore classified for 'general use'.

APPENDIX

CHEMICAL DATA SHEETS

Chemical Data Sheets have been prepared for the components, hydrolysis products, and known metabolites of manufacturing-use Metolachlor. The Data Sheets are divided into Components COM001 through COM011, Hydrolysis Products HP001 and HP002, and Metabolites MET001 through MET024. Chemical Data Sheets are not available for MET025 and MET026, though their structures are given in the Environmental Fate chapter.

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COMPONENT NUMBER COM001

01. Chemical Abstracts Chemical names;

01 Acetamide, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)-(CA9)

02 *o*-Acetotoluidide, 2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)-(CA8)

02. Other Chemical Names;

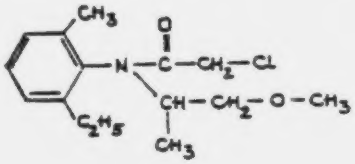
01 2-Chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2'-methoxy-1'-methylethyl)-acetamide

02 Acetanilide, 2-chloro-2'-ethyl-N-(2-methoxy-1-methylethyl)-6'-methyl-

03 N-(2'-Methoxy-1'-methylethyl)-2-ethyl-6-methyl-chloroacetanilide

04 N-(Chloroacetyl)-6-ethyl-N-(2-methoxyisopropyl)-*o*-toluidine

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{15}H_{22}ClNO_2$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name;

01 Metolachlor

07. Other Common Names, Trade Names, or Codes;

01 Dual

02 CGA No. 24705

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Chemical Data Sheets COM-002 through COM-011 have been omitted in this Sample Registration Standard because of confidentiality claims by the manufacturer.

HYDROLYTIC PRODUCT NUMBER HP001

01. Chemical Abstracts Chemical Names;

01 1-Propanol, 2-[(2-ethyl-6-methylphenyl)amino]- (CA9)

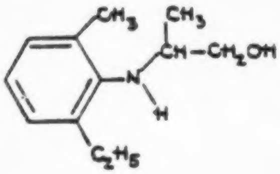
02 1-Propanol, 2-(6-ethyl-o-toluidino)- (CA8)

02. Other Chemical Names;

01 1-Propanol, 2-(2-ethyl-6-methylanilino)-

02 2-[(2-Ethyl-6-methyl)amino]-1-propanol

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{12}H_{19}NO$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 37913

02 PHP (Propanol hydrolytic product)

HYDROLYTIC PRODUCT NUMBER HP002

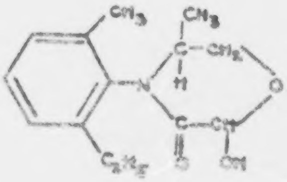
01. Chemical Abstracts Chemical Names;

01 3-Morpholinone, 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-

02 3-Morpholinone, 4-(6-ethyl-o-tolyl)-2-hydroxy-5-methyl-

02. Other Chemical Names;
01 4-(2-Ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{14}H_{19}NO_3$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 49751

02 MHP (morpholinone hydrolytic product)

METABOLITE NUMBER MET001

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-2-hydroxy-N-(2-methoxy-1-methylethyl)- (CA9)

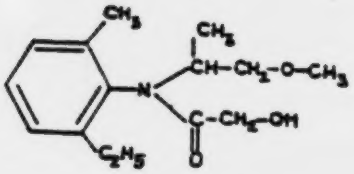
02 o-Acetotoluidide, 6'-ethyl-2-hydroxy-N-(2-methoxy-1-methylethyl)-(CA8)

02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-2-hydroxy-N-(2-methoxy-1-methylethyl)-6'-methyl-

02 N-(2-Ethyl-6-methylphenyl)-2-hydroxy-N-(2-methoxy-1-methylethyl)acetamide

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{15}H_{23}NO_3$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 40172

METABOLITE NUMBER MET002

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-2-hydroxy- (CA9)

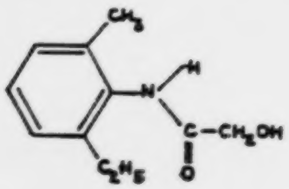
02 *o*-Acetotoluidide, 6'-ethyl-2-hydroxy-(CA8)

02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-2-hydroxy-6'-methyl-

02 *N*-(2-Ethyl-6-methylphenyl)-2-hydroxyacetamide

Structural Formula;



04. Molecular (Empirical) Formula;

$C_{11}H_{15}NO_2$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 37735

METABOLITE NUMBER MET003

01. Chemical Abstracts Chemical Names;

01 Acetamide, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methylethyl)- (CA9)

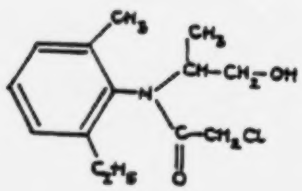
02 o-Acetotoluidide, 2-chloro-6'-ethyl-N-(2-hydroxy-1-methylethyl)- (CA8)

02. Other Chemical Names;

01 Acetanilide, 2-chloro-2'-ethyl-N-(2-hydroxy-1-methylethyl)-6'-methyl-

02 2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methylethyl)acetamide

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{14}H_{20}ClNO_2$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 41638

METABOLITE NUMBER MET004

01. Chemical Abstracts Chemical Names;

01 DL-Alanine, N-(2-ethyl-6-methylphenyl)-N-(hydroxyacetyl)- (CA9)

02 DL-Alanine, N-(6-ethyl-o-tolyl)-2-(hydroxyacetyl)- (CA8)

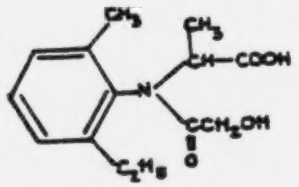
02. Other Chemical Names;

01 Propanoic acid, 2-[N-(2-ethyl-6-methylphenyl)-2-hydroxyacetamido]-

02 Propionic acid, 2-[N-(6-ethyl-o-tolyl)-2-hydroxyacetamido]-

03 N-(2-Ethyl-6-methylphenyl)-N-(hydroxyacetyl)alanine

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{14}H_{19}NO_3$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 46129

METABOLITE NUMBER MET005

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)-(CA9)

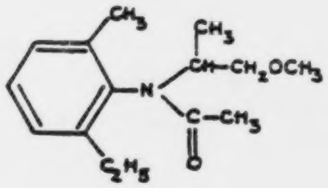
02 o-Acetotoluidide, 6'-ethyl-N-(2-methoxy-1-methylethyl)- (CA8)

02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-N-(2-methoxy-1-methylethyl)-6'-methyl-

02 N-(2-Ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{15}H_{23}NO_2$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 Dechlorometolachlor

02 CGA No. 41507

METABOLITE NUMBER MET006

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methylethyl)- (CA9)

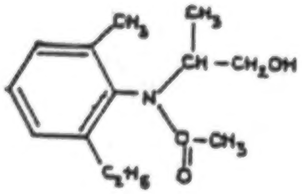
02 *o*-Acetotoluidide, 6'-ethyl-N-(2-hydroxy-1-methylethyl)- (CA8)

02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-N-(2-hydroxy-1-methylethyl)-6'-methyl-

02 *N*-(2-Ethyl-6-methylphenyl)-*N*-(2-hydroxy-1-methylethyl)acetamide

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{14}H_{21}NO$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 42446

METABOLITE NUMBER MET007

01. Chemical Abstracts Chemical Names;

    01 Acetamide, N-(2-ethyl-6-methylphenyl)- (CA9)

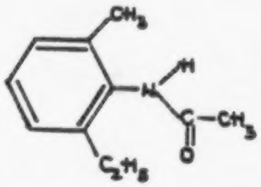
    02 o-Acetotoluidide, 6'-ethyl- (CA8)

02. Other Chemical Names;

    01 Acetanilide, 2'-ethyl-6'-methyl-

    02 N-(2-Ethyl-6-methylphenyl)acetamide

03. Structural Formula;



04. Molecular (Empirical) Formula;

    $C_{11}H_{15}NO$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

    01 CGA No. 42444

METABOLITE NUMBER MET008

01. Chemical Abstracts Chemical Names;

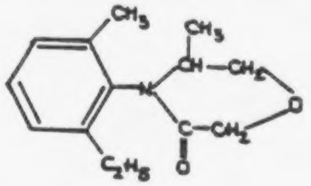
01 3-Morpholinone, 4-(2-ethyl-6-methylphenyl)-5-methyl- (CA9)

02 3-Morpholinone, 4-(6-ethyl-o-tolyl)-5-methyl- (CA8)

02. Other Chemical Names;

01 4-(2-Ethyl-6-methylphenyl)-5-methyl-3-morpholinone

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{14}H_{19}NO_2$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 40919

METABOLITE NUMBER MET009

01. Chemical Abstracts Chemical Names;

01 Acetamide, 2-chloro-N-(2-ethyl-6-methylphenyl)- (CA9)

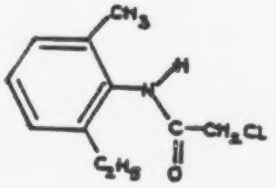
02 o-Acetotoluidide, 2-chloro-6'-ethyl- (CA8)

02. Other Chemical Names;

01 Acetanilide, 2-chloro-2'-ethyl-6'-methyl

02 2-Chloro-N-(2-ethyl-6-methylphenyl)acetamide

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{11}H_{14}ClNO$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 13656

METABOLITE NUMBER MET010

01. Chemical Abstracts Chemical Names;

01 Benzenamine, 2-ethyl-N-(2-methoxy-1-methylethyl)-6-methyl- (CA9)

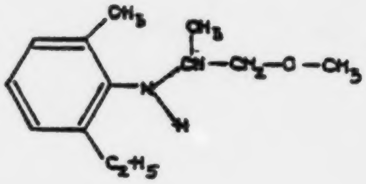
02 o-Toluidine, 6-ethyl-N-(2-methoxy-1-methylethyl)- (CA8)

02. Other Chemical Names;

01 Aniline, 6-ethyl-N-(2-methoxy-1-methylethyl)-6-methyl-

02 2-Ethyl-N-(2-methoxy-1-methylethyl)-6-methylbenzenamine

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{13}H_{21}NO$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 CGA No. 38502

METABOLITE NUMBER MET011

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-2-mercapto-N-(2-methoxy-1-methylethyl)-,S-conjugate with Glutathione

02 o-Acetotoluidide, 2'-ethyl-2-mercapto-N-(2-methoxy-1-methylethyl)-, S-conjugate with Glutathione

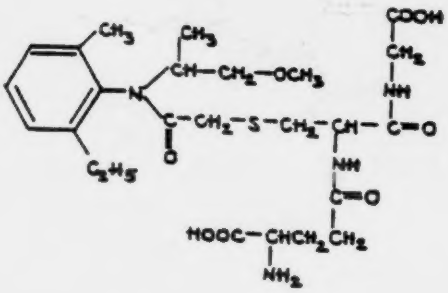
02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-2-mercapto-N-(2-methoxy-1-methylethy)-6'-methyl-,S-conjugate with Glutathione

02 Glutathione, sulfide with 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide

03 Glutathione, sulfide with 2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)-o-acetotoluidide

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{25}H_{38}N_4O_8S$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 Metolachlor glutathione conjugate

02 CGA No. 43826

METABOLITE NUMBER MET012

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-2-mercapto-N-(2-methoxy-1-methylethyl)-,S-conjugate with Glucuronic acid (CA9)

02 o-Acetotoluidide, 2'-ethyl-2-mercapto-N-(2-methoxy-1-methylethyl)-, S-conjugate with Glucuronic acid (CA8)

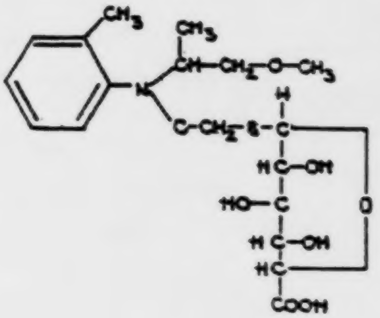
02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-2-mercapto-N-(2-methoxy-1-methylethyl)-6'-methyl-,S-conjugate with Glucuronic acid

02 Glucuronic acid, 1-S-[[[(2-ethyl-6-methylphenyl)(2-methoxy-1-methylethyl)-amino]carbonyl]methyl]-1-thio-

03 Glucuronic acid, 1-S-[[(6-ethyl-o-tolyl)(2-methoxy-1-methylethyl)carbamoyl]methyl]-1-thio-

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{21}H_{30}NO_8S$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 Metolachlor glucuronic acid conjugate

02 Compound N

METABOLITE NUMBER MET013

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methylethyl)-2-mercapto-, 0-glucoside, S-conjugate with Glucuronic acid (CA9)

02 o-Acetotoluidide, 6'-ethyl-N-(2-hydroxy-1-methylethyl)-2-mercapto-, 0-glucoside, S-conjugate with Glucuronic acid (CA8)

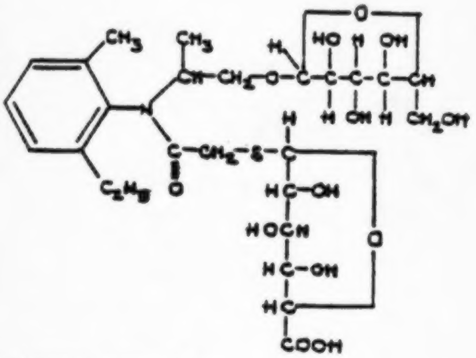
02. Other Chemical Names;

01 Acetanilide, 2'ethyl-N-(2-hydroxy-1-methylethyl)-2-mercapto-6'-methyl-, 0-glucoside, S-conjugate with Glucuronic acid

02 Glucuronic acid, 1-S-[[(6-ethyl-o-tolyl)(2-glucosyl(1)-1-methylethyl)carbamoyl]methyl]-1-thio-

03 Glucuronic acid, 1-S-[[[(2-ethyl-6-methylphenyl)(2-glucosyl(1)-1-methylethyl)amino]carbonyl]methyl]-1-thio-

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{26}H_{39}NO_{13}S$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 Compound No. 0

METABOLITE NUMBER MET014

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methoxyethyl)-2-mercapto-, S-conjugate with Glucuronic acid (CA9)

02 o-Acetotoluidide, 2'-ethyl-N-(2-hydroxy-1-methylethyl)-2-mercapto-, S-conjugate with Glucuronic acid (CA8)

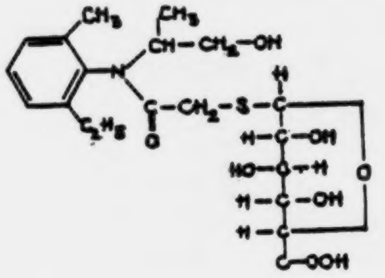
02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-N-(2-hydroxy-1-methylethyl)-2-mercapto-6'-methyl-, S-conjugate with Glucuronic acid

02 Glucuronic acid, 1-S-[[[(2-ethyl-6-methylphenyl)(2-hydroxy-1-methylethyl)amino]carbonyl]methyl]-1-thio-

03 Glucuronic acid, 1-S-[[(6-ethyl-o-tolyl)(2-hydroxy-1-methylethyl)carbamoyl]methyl]-1-thio-

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{20}H_{28}NO_8S$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 Demethylmetolachlor glucuronic acid conjugate

METABOLITE NUMBER MET015

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-2-hydroxy-N-(2-methoxy-1-methylethyl)-, O-conjugate with Glucuronic acid (CA9)

02 o-Acetotoluidide, 2'-ethyl-2-hydroxy-N-(2-methoxy-1-methylethyl)-, O-conjugate with Glucuronic acid (CA8)

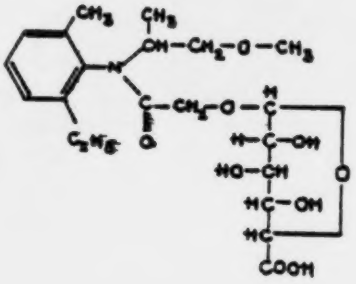
02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-2-hydroxy-N-(2-methoxy-1-methylethyl)-6'-methyl-, O-conjugate with Glucuronic acid

02 Glucuronic acid, 1-0-[[[(2-ethyl-6-methylphenyl)(2-methoxy-1-methylethyl)amino]carbony]methyl]-

03 Glucuronic acid, 1-0-[[(6-ethyl-o-tolyl)(2-methoxy-1-methylethyl)-carbamoyl]methyl]-

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{21}H_{31}NO_9$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 Metolachlor glucuronic acid conjugate

METABOLITE NUMBER MET016

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-2-hydroxy-N-(2-hydroxy-1-methylethyl)-, O-conjugate with Glucuronic acid

02 o-Acetotoluidide, 2'-ethyl-2-hydroxy-N-(2-hydroxy-1-methylethyl)-, O-conjugate with Glucuronic acid

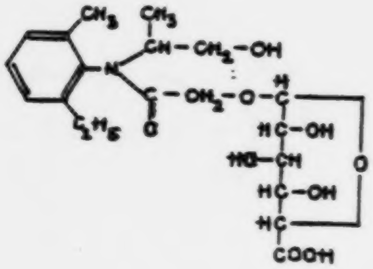
02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-2-hydroxy-N-(2-hydroxy-1-methylethyl)-6'-methyl-, O-conjugate with Glucuronic acid

02 Glucuronic acid, 1-O-[[[(2-ethyl-6-methylphenyl)(2-hydroxy-1-methylethyl)amino]carbonyl]methyl]-

03 Glucuronic acid, 1-O-[[(6-ethyl-o-tolyl)(2-hydroxy-1-methylethyl)-carbamoyl]methyl]-

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{20}H_{29}NO_9$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes;

01 Desmethylmetolachlor glucuronic acid conjugate

METABOLITE NUMBER MET017

01. Chemical Abstracts Chemical Names;

01 Acetamide, N-(2-ethyl-6-methylphenyl)-2-hydroxy-N-(2-hydroxy-1-methylethyl)-, 0-glucoside, O-conjugate with Glucuronic acid (CA9)

02 o-Acetotoluidide, 6'-ethyl-2-hydroxy-N-(2-hydroxy-1-methylethyl)-, O-glucoside, O-conjugate with Glucuronic acid (CA8)

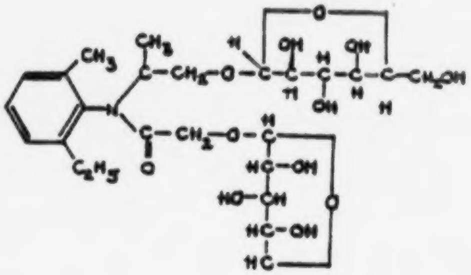
02. Other Chemical Names;

01 Acetanilide, 2'-ethyl-2-hydroxy-N-(2-hydroxy-1-methylethyl)-6'-methyl-,0-glucoside, O-conjugate with Glucuronic acid

02 Glucuronic acid, 1-0-[[(6-ethyl-o-tolyl)(2-glucosyl(1)-1-methylethyl)-carbamoyl]methyl]

03 Glucuronic acid, 1-0-[[[((2-ethyl-6-methylphenyl)(2-glucosyl(1)-1-methylethyl)amino]carbonyl]methyl]-

03. Structural Formula;



04. Molecular (Empirical) Formula;

$C_{26}H_{39}NO_{14}$

05. Chemical Abstracts (CAS) Registry Number;

06. Approved Common Name; None

07. Other Common Names, Trade Names, or Codes; None

METABOLITE NUMBER: 018

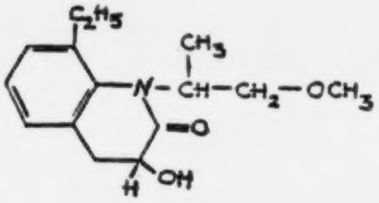
01. Chemical Abstracts Chemical Names:

01 Quinoline, N-(2-methoxy-1-methylethyl)-8-ethyl-3-hydroxy-2-oxo-1,2,3,4-tetrahydro-

02. Other Chemical Names:

01 8-Ethyl-3-hydroxy-N-(2-methoxy-1-methylethyl)-2-oxo-1,2,3,4-tetrahydroquinoline

03. Structural Formula:



04. Molecular (Empirical) Formula:

$C_{15}H_{21}NO_3$

05. Chemical Abstracts (CAS) Registry Number:

06. Approved Common Names, Trade Names, or Codes:

METABOLITE NUMBER: 019

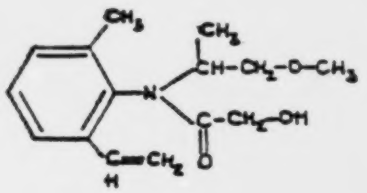
01. Chemical Abstracts Chemical Names:

01 Acetamide, 2-hydroxy-N-(2-methyl-6-vinylphenyl)-N-(2-methoxy-1-methylethyl)-

02. Other Chemical Names:

01 2-hydroxy-N-(2-mothyl-6-vinylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

03. Structural Formula:



04. Molecular (Empirical) Formula:

$C_{15}H_{21}NO_3$

05. Chemical Abstracts (CAS) Registry Number:

06. Approved Common Names: None

07. Other Common Names, Trade Names, or Codes:

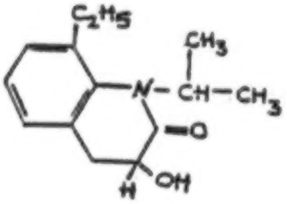
01. Chemical Abstracts Chemical Names:

01 Quinoline, N-isopropyl-8-ethyl-3-hydroxy-2-oxo-1,2,3,4,-tetrahydro-

02. Other Chemical Names:

01 8-Ethyl-3-hydroxy-N-isopropyl-2-oxo-1,2,3,4-tetrahydroquinoline

03. Structural Formula:



04. Molecular (Empirical) Formula:

$C_{14}H_{19}NO_2$

05. Chemical Abstracts (CAS) Registry Number:

06. Approved Common Names: None

07. Other Common Names, Trade Names, or Codes:

METABOLITE NUMBER: 021

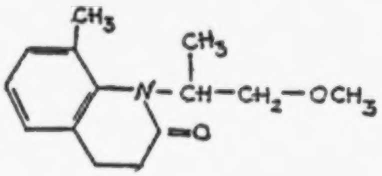
01. Chemical Abstracts Chemical Names:

01 Quinoline, 8-methyl-N-(2-methoxy-1-methylethyl)-2-oxo-1,2,3,4-tetrahydro

02. Other Chemical Names:

01 8-Methyl-N-(2-methoxy-1-methylethyl)-2-oxo 1,2,3,4-tetrahydroquinoline

03. Structural Formula:



04. Molecular (Empirical) Formula:

$C_{14}H_{19}NO_2$

05. Chemical Abstracts (CAS) Registry Number:

06. Approved Common Names: None

07. Other Common Names, Trade Names, or Codes:

METABOLITE NUMBER: 022

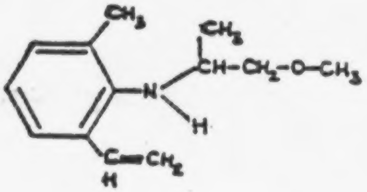
01. Chemical Abstracts Chemical Names:

01 Aniline, N-(2-methoxy-1-methylethyl)-2-methyl-6-vinyl-

02. Other Chemical Names:

01 N-(2-methoxy-1-methylethyl)-(2-methyl-6-vinyl) aniline

03. Structural Formula:



04. Molecular (Empirical) Formula:

$C_{13}H_{19}NO$

05. Chemical Abstracts (CAS) Registry Number:

06. Approved Common Names: None

07. Other Common Names, Trade Names, or Codes:

METABOLITE NUMBER: 023

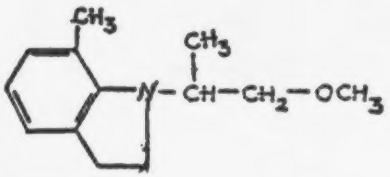
01. Chemical Abstracts Chemical Names:

01 Indole, 2,3-dihydro-N-(2-methoxy-1-methylethyl)-7-methyl-

02. Other Chemical Names:

01 N-(2-methoxy-1-methylethyl)-7-methyl-2,3-dihydroindole aniline

03. Structural Formula:



04. Molecular (Empirical) Formula:

$C_{13}H_{19}NO$

05. Chemical Abstracts (CAS) Registry Number:

06. Approved Common Names: None

07. Other Common Names, Trade Names, or Codes:

METABOLITE NUMBER: 024

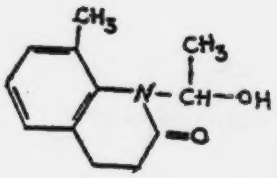
01. Chemical Abstracts Chemical Names:

01 Quinoline, N-(1-hydroxyethyl)-8-methyl-2-oxo-1,2,3,4-tetrahydro-

02. Other Chemical Names:

01 8-Methyl-N-(1-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinoline

03. Structural Formula:



04. Molecular (Empirical) Formula:

$C_{12}H_{15}NO_2$

05. Chemical Abstracts (CAS) Registry Number:

06. Approved Common Names: None

07. Other Common Names, Trade Names, or Codes:

BIBLIOGRAPHY

GUIDE TO THE USE OF THIS BIBLIOGRAPHY

Content of the Bibliography

This bibliography contains citations of all the studies reviewed by EPA in arriving at the positions and conclusions stated elsewhere in this Standard. The two primary sources for these studies were: (a) the body of data submitted to EPA and its predecessor agencies in support of pest regulatory decisions on pesticide registration, and (b) published technical literature. The bibliography cites and distinguishes between three types of studies:

(1) Studies which were found to contribute useful information to the Agency's review of Metolachlor and are considered part of the data base which supports registrations under this Standard. (Each of these studies also appears in one or more of the Disciplinary Chapter bibliographies.) These studies are identified by an asterisk (*) placed beside their citation.
(2) Studies which were examined and judged to be inappropriate for use in developing the Standard. These studies do not have any mark placed beside their citation.
(3) Standard reference materials. These materials are identified by a small circle (o) placed beside their citation.

Units of Entry

The unit of entry in this bibliography is called a "study". In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the Agency, we have sought to identify documents at a level parallel to a published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review, and can be described with a conventional bibliographic citation. We have also attempted to unite basic documents and commentaries upon them, treating them together as a single study.

Form of the Entry

The entries in the bibliography are sorted by author, date of the document, and title. Each entry consists of a bibliographic citation containing standard elements. In the case of materials submitted to EPA, these elements are followed by a description of the earliest known submission. The bibliographic conventions used reflect the standards of the American National Standards Institute (ANSI), explanded to provide for special needs. Some explanatory notes of specific elements follow:

(a) Author. Whenever we could confidently identify one, we have chosen to show a personal author. When no individual was identified, we have shown an identifiable laboratory or testing facility as author. As a last resort, we have shown the first known submitter as author.
(b) Document Date. When the date appears as four digits with no question marks, we took it directly from the document. When a four digit date is followed by a question mark, the bibliographer deduced the date from evidence in the document. When the date appears (19??), we were unable to determine or estimate the date of the document.

Preceding page blank

(c) Title. This is the third element in the citation. In some cases it has been necessary for our bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

(d) Trailing Parentheses. For studies submitted to us in the past, the trailing parentheses include (in addition to any self-explanatory text) the following elements describing the earliest known submission:

    (1) Submission Date. Immediately following the word 'received' appears the date of the earliest known submission.

    (2) Administrative Number. The next element, immediately following the word 'under', is the registration number, experimental permit number, petition number, or other administrative number associated with the earliest known submission.

    (3) Preparer and/or Submitter. Following the phrase 'prepared by' is the name of the facility which conducted the study or reported its results, and following the phrase 'prepared for' is the name of the submitter who submitted the data to support some application or petition.

    (4) Volume Identification. The final element in the trailing parentheses identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol 'CDL', which stands for "Company Data Library." This accession number is in turn followed by an alphabetic suffix which shows the relative posiution of the study within the volume. For example, within accession number 123456, the first study would be 123456-A; the second, 123456-B; the 26th, 123456-Z; and the 27th, 123456-AA.

* Affiliated Medical Research, Incorporated (1974a) Acute Dermal LD_{50} of CGA-24705 - Technical in Rabbits: Contract No. 120-2255-34. (Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-E)

Affiliated Medical Research, Incorporated (1974b) Acute Dermal LD_{50} of CGA-24705-6E: Contract No. 12-2255-34. Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-F)

Affiliated Medical Research, Incorporated (1974c) Acute Inhalation Study of CGA-24705-6E for Albino Rats: Contract No. 121-2253-34. Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-M)

Affiliated Medical Research, Incorporated (1974d) Acute Oral Toxicity in Rats of CGA-24705-6E: Contract No. 121-2255-34. (Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-B)

* Affiliated Medical Research, Incorporated (1974e) Emetic Dose 50 in Beagle Dogs with CGA-24705-Technical: Contract No. 120-2255-34. (Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-C)

* Affiliated Medical Research, Incorporated (1974f) Emetic Dose 50 in Beagle Dogs with CGA-24705-6E: Contract No. 121-2255-34.(Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-D)

* Affiliated Medical Research, Incorporated (1974g) Evaluation of CGA-24705 Technical (FL740408) as a Potential Skin Sensitizer in the Guinea Pig: Contract No. 120-2255-34. (Unpublished study received Sep 26, 1977 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-K)

Affiliated Medical Research, Incorporated (1974h) Primary Dermal Irritation of CGA-24705-6E in Albino Rabbits: Contract No. 121-2255-34. (Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-J)

Affiliated Medical Research, Incorporated (1974i) Primary Eye Irritation of CGA-24705-6E in Albino Rabbits: Contract No. 121-2255-34. (Unpublished study received Sep 26, 1974 under 5G1553; prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL:112840-H)

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Ciba-Geigy Corporation (1977au) M+A 4.5L - Preplant Incorporated. (Unpublished study containing reports 1-50 with a summary, 1C-9C with a summary, and 1D-12D with a summary; received Jun 20, 1977 under 100-590; CDL:230672-B, 230678, 230679, 230680, 230681)

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